ORGANOSULFUR REACTIONS IN ORGANIC SYNTHESIS WITH METAL SULFUR DERIVATIVES (M=Mo,W)

A Thesis Submitted
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by
PREETI DHAR

to the
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NOVEMBER, 1989

IN THE LOVING MEMORY

OF MY GRANDMOTHER

SMT. MOGALANI DHAR

DEPARTMENT OF CHEMISTRY
INDIAN INSTITUTE OF TECHNOLOGY KANPUR, INDIA

CERTIFICATE OF COURSE WORK

This is to certify that Miss Preeti Dhar has satisfactorily completed all the courses required for the Ph.D. degree program. The courses include:

Chm 505 Principles of Organic Chemistry
Chm 511 Physical Organic Chemistry
Chm 524 Modern Physical Methods in Chemistry
Chm 525 Principles of Physical Chemistry
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Chm 900 Post-Graduate Research

Miss Preeti Dhar was admitted to the candidacy of the Ph.D. degree in March 1986 after she successfully completed the written and oral qualifying examinations.

(P. S. Goel)
Professor and Head,
Department of Chemistry
I.I.T. Kanpur

for (P. K. Bharadwaj)
Convener, Departmental Post-Graduate Committee, Dept. of Chemistry, I.I.T. Kanpur

CERTIFICATE

Certified that the work contained in this thesis entitled "ORGANO SULFUR REACTIONS IN ORGANIC SYNTHESIS WITH METAL SULFUR DERIVATIVES (M = Mo, W)" has been carried out by Miss Preeti Dhar under my supervision and the same has not been submitted elsewhere for a degree.

S. CHANDRASEKARAN
Thesis Supervisor

STATEMENT

I hereby declare that the matter embodied in this thesis, entitled: "ORGANOSULFUR REACTIONS IN ORGANIC SYNTHESIS WITH METAL SULFUR DERIVATIVES (M = Mo, W)", is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology, Kanpur, India, under the supervision of Professor S. Chandrasekaran.

In keeping with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigators.

PREETI DHAR

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PREETI DHAR

PREFACE

The thesis entitled "ORGANOSULFUR REACTIONS IN ORGANIC SYNTHESIS WITH METAL SULFUR DERIVATIVES (M = Mo, W)" consists of four chapters.

Chapter I of the thesis gives a general account of the chemistry of thiometallates and disulfides and describes a novel alkylation reaction of tetrathiometallates [MS_4^{2-}] **6** of tunsten and molybdenum with alkyl halides. Reaction of piperidinium tetrathiotungstate or piperidinium tetrathiomolybdate with alkyl halides in dimethyl formamide at room temperature for 0.5-1 h gave the corresponding disulfides in excellent yield. Although a number of methods are available in the literature for disulfide bond formation, the search for milder reagents for the operationally simple process is still on. We have developed a very simple route for the synthesis of disulfides directly from the corresponding alkyl halides.

In the present work this method has been applied successfully in the preparation of variety of disulfides from primary, secondary and benzylic halides. Tertiary halides are inert to this complex. The alkyl tosylates react with tetrathiometallates **6** to give the corresponding disulfides in good yield though the reaction of tosylates with this complex is much slower (12-15 h). The order of reactivity: alkyl iodide > alkyl bromide > alkyl chloride > alkyl tosylate is in line with the softness of the sulfur nucleophile. Aryl halides **30** are not

affected by tetrathiometallates **6** under the reaction conditions.

Benzyl chloride **7a** gave a slightly higher proportion of the minor product, thiol **8a** compared to benzyl bromide **7b**. On the other hand benzyl iodide **7c** afforded the disulfide **8** as the exclusive product in high yield. The reaction of the benzyl halides having electron withdrawing substituents was faster when compared to those having electron donating substituents. In the reaction of simple alkyl bromides with piperidinium tetrathiotungstate **6a**, it was seen that primary bromides reacted faster than secondary bromides. In all the reaction of alkyl halides with piperidinium tetrathiomolybdate **6b**, disulfides were the only product obtained in high yield. On the basis of the product(s) obtained, two tentative mechanisms for this novel alkylation have been outlined.

This new methodology is equally effective for carrying out intramolecular reactions. This forms the subject matter of Chapter II. 1,3-Dibromobutane **7** reacts with tetrathiotungstate **6** at room temperature to give a dimer **8** When the same reaction is carried out at a slightly elevated temperature (60 ^{o}C) for 4 h, we get the corresponding dithiolane **9** as the sole product. This method has been effectively used to construct cyclic five, six, seven and eight membered disulfides. The effectiveness of this methodology has also been extended to the synthesis of disulfides in spirocyclic ring system. Accordingly, pentaerythritol tetrabromide **23** was treated with two equivalents of tetrathiotungstate **6** to give

the corresponding spiro compound **24** in good yield. 3,5-Dibromocyclopentene **25**, when treated with tetrathio-tungstate **6** at 0 ^{o}C gave the corresponding highly volatile bicyclic disulfide **26**. This could prove to be an important intermediate for the synthesis of dithia-analogue of prostaglandin.

Application of this methodology has been extended to the synthesis of two natural products having dithiolane ring system. The key step in the synthesis of these natural products is the disulfide bond formation. The two natural products which have been synthesized using this strategy are asparagusic acid **41** and α-lipoic acid **37**.

α-Lipoic acid **37** is one of the coenzymes of an enzyme complex that catalyzes oxidative decarboxylation of α-keto-carboxylic acids. Although a large number of synthesis of lipoic acid have been reported in the literature, invariably all of them use Na_2S_2 for forming the disulfide linkage which is also the key step of the synthesis. The reaction conditions are not that mild and the yields of the products are only moderate. Our methodology was applied efficiently in the synthesis of lipoic acid **37**. This was prepared in six steps starting from acetoacetic ester.

Asparagusic acid **41**, a plant growth inhibitor having the dithiolane ring system was prepared in three steps starting from diethylmalonate.

Chapter III of the thesis deals with the reductive coupling of sulfonyl halides and derivatives with tetrathiotungstate **6**. Sulfonyl halides **1**, sulfinyl halide **2**, sulfenyl halide **3**, sulfinic acid **16**, α-disulfones **7** and thiosulfonates **5** are reduced to the corresponding disulfides using tetrathiotungstate **6**. Sulfonic acid **19**, sulfones **18** and sulfoxides **17** are inert to this reagent. Some of the postulated intermediates have been synthesized and shown to be converted to final products.

Chapter IV of the thesis deals with the generation of highly reactive singlet diatomic sulfur species using tetrathiotungstate **6** and its trapping using various dienes. 9,10-Dibromo-9,10-dihydroanthracene **14** when treated with tetrathiotungstate **6** forms anthracene endo disulfide **18** *in situ* which then decomposes to singlet sulfur and anthracene. This singlet sulfur has been trapped using cyclopentadiene **25**, isoprene **22** and 2,3-diphenylbutadiene **20** in a (4+2) cycloaddition reaction.

CONTENTS

CHAPTER I

NOVEL ALKYLATION OF ALKYL HALIDES USING TETRATHIOMETALLATES (M = Mo, W)

1.1 INTRODUCTION

1.1a Thiometallates

Recent years have seen dramatic expansion in synthetic and structural molybdenum/tungsten-sulfur chemistry.[1] Current developments in M-S (where M = Mo, W) serve to demonstrate the structural diversity possible for combination of these elements. The simplest binary M-S moiety is the $[MS_4]^{2-}$ ion. The molybdates $[MoO_4]^{2-}$ and tungstates $[WO_4]^{2-}$ undergo partial or total substitution of oxygen by sulfur. The thiomolybdates and thiotungstates derived by sulfur substitution from the oxo analog have interesting chemical properties and occupy a special position in coordination chemistry as they are unique ligands which are purely inorganic in nature and give rise to sulfur bridged multi-metallic complexes.

The first report on thiomolybdates appeared in literature as early as 1826, when Berzelius investigated their formation by passing H_2S gas into aqeuous solutions of molybdates or tungstates.[2] Sixty years later Kruss[3] and Corleis[4] reported

the synthesis of $(NH_4)_2MoS_4$ and $(NH_4)_2WS_4$, respectively. Detailed studies on the chemistry of these species had however not begun until the late 1960. Since then, Müller and coworkers, have done pioneering work on the chemistry of these anions and particularly on their ability to behave as bidentate ligands.[5,6]

Thiomolybdate and thiotungstate anions are prepared by the reactions of oxo-molybdate or oxo-tungstate anions with H_2S in basic aqueous solutions.[7,8] The reaction can be represented as follows:

$$[MO_4]^{2-} \xrightarrow{H_2O} [MO_3S]^{2-} \xrightarrow{H_2S} [MO_2S_2]^{2-}$$

$$\xrightarrow{H_2S} [MOS_3]^{2-} \xrightarrow{H_2S} [MS_4]^{2-}$$

where M = Mo, W.

All the thiometallates [the term thiometallate refers to any of the thioanions of the formula $[(MO_{4-n}S_n)^{2-}$ where n = 1-4] have strong and characteristic absorption bands in the UV-VIS region and hence the reaction in which they are formed or decomposed can be followed by spectroscopic methods.[7]

The duration of passage of hydrogen sulfide gas, the temperature, the concentration and the counter cation used are all important factors to be considered for the preparation and isolation of various thiometallates. The monothioanions have been shown to exist only in solution and pure compounds have

not been isolated.[9,10] The dithiometallates are prepared from cold oxometallate solutions. The trithiometallate can be easily prepared as cesium salts. The $[MoO_4]^{2-}$ ion forms the tetrathio species readily, while preparation of tetrathiotungstate requires drastic conditions (60 °C, 9 hr).[8] The stability of the thiometallates decreases with increasing oxygen content. Thus the dithiometallates are readily hydrolyzed by water. Further, the thiometallates are not very stable in aqueous solutions, especially at low pH. The $[MS_4]^{2-}$ is tetrahedral like the $[SO_4]^{2-}$ ion.[11-13] Ammonium tetrathiometallates decompose to give ammonia, H_2S and the amorphous trisulfide, when heated[14,15](Eqn. 1.1):

$$(NH_4)_2MS_4 \longrightarrow 2\ NH_3 + H_2S + MS_3 \qquad ..(1.1)$$

The thiometallates are versatile reagents in inorganic synthesis and undergo a variety of reactions with various reagents. These reactions can be broadly classified into two types:

(i) Reaction of thiometallates resulting in the formation of sulfur rich polythiometallates.

(ii) Reactions of thiometallates resulting in the formation of heterometal aggregates.

(i) <u>Formation of Polythiometallates</u>

The polythiometallates are formed by the reaction of thiometallates with (a) polysulfides,[16-19](b) elemental

sulfur,[20-28] (c) organic disulfides,[29-31] (d) thiols[32,33] and (e) acids.[6,33-37] A number of polythiometallates have been synthesized and structurally characterized in recent years. The facile formation of these sulfur rich species is a clear indication of the high affinity of molybdenum or tungsten in different oxidation states for sulfur.

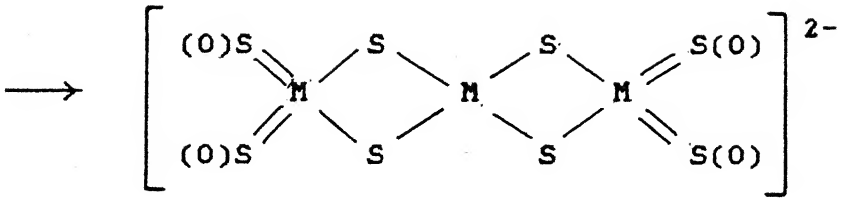
$[WS_4]^{2-}$ unlike $[MoS_4]^{2-}$ does not react with polysulfide. The condensation behavior of $[WS_4]^{2-}$ differs considerably from that of $[MoS_4]^{2-}$ since protonation takes place at relatively low pH values.

(ii) Formation of Heterometal Aggregates

The utility of tetrathiometallate as purely inorganic chelating ligands started with the reported synthesis of bis-(tetrathiotungstato)nickelate(II) anion $[Ni(WS_4)_2]^{2-}$.[38] Müller and coworkers studied the ligational behavior of the thiometallates and synthesized several heteronuclear complexes where the central metal ion can either be a transition metal or a non-transition metal and the thiometallate can be any member of the series $(MS_{4-n}O_n)^{2-}$ [M = Mo, W; n = 0-2].[5,6,39-46]

The preparation of the bis(thiometallato) complexes involves the reaction of bivalent metal salts in the presence of bulky cation with thiometallates in aqueous medium. The general reaction for the formation of bis(thiometallato) metal complexes can be written as follows:

$$M'^{2+} + 2(XR_4)^+ + 2(MS_{4-n}O_n)^{2-}$$



..(1.2)

where M' = Fe, Co, Ni, Pd, Pt, Zn, Cd, Hg

M = Mo, W

X = As, P

n = 0, 1, 2

The following points have been observed in the above reactions:

(i) Bulky cations are essential to trap the dinegative complex anions.[39]

(ii) When thiomolybdates are used, in addition to complex formation there is also the formation of amorphous products which necessiates purification steps.[41]

(iii) The central metal is tetracoordinated and the coordination is always through the sulfur end in all the cases.[42,43]

(iv) The combination M' = Fe and M = Mo does not form any discrete bis(thiometallato) complex.[45]

(v) Depending on the nature of the central metal atom there can be square planar or tetrahedral arrangement of sulfur atoms around heterometal. Thus the bis(thiometallate) complexes of Ni(II),[47] Pd(II) and Pt(II)[46] are square planar while those of Fe(II), Co(II)[48] and Zn(II)[49] are

tetrahedral.

The interest in the thiometallate complexes of Co & Ni is mainly due to the relevance of [M'-M-S] [M' = Co, Ni] systems in hydrodesulfurization (HDS) catalysts.[50]

The Cu-thiometallate chemistry has been studied in detail in an effort to understand the chemical implications of Cu-Mo antagonism and has been reviewed recently by Sarkar and Mishra.[51]

Very little work has been done in the area of the thiometallate complexes of 4d and 5d metals. The square planar bis-(thiometallato) complexes of Pd and Pt are well known.[46] The chemistry of the thiometallates with organometallic complexes of ruthenium and rhodium has been studied by Rauchfuss and coworkers.[52]

Biological Significance

The relevance of thiomolybdates, $[MoS_nO_{4-n}]^{2-}$ (n = 1-4), and particularly of MoS_4^{2-} in some biological processes has recently been recognised. The synthesis and characterization of iron-thiometallate [Fe-M-S] (M = Mo, W) complexes as structural models for the molybdenum site of nitrogenase has been the subject of intense investigations of many researchers. The chemistry of [Fe-M-S] complexes derived from $[MS_4]^{2-}$ anions (M = Mo, W) has been reviewed by Coucouvanis[53] and Averill.[54] The iron-molybdenum cofactor [Fe-Mo-Co] isolated from Fe-Mo

component protein of nitrogenase consists of approximately 2 molybdenums, 28-32 irons and 30 acid labile sulfurs.[55] The molybdenum K-edge EXAFS analysis of the Fe-Mo-Co has shown the presence of a unique [Fe-Mo-S] aggregate with four or five sulfur atoms around the molybdenum as well as two or three iron atoms in the second coordination sphere.[56,57] The isolation of MoS_4^{2-} by the acid/base hydrolysis of Mo-Fe protein of Clostridium pasteuranim in 1978 by Zumft[58] had particular impact on the rapid development of the chemistry of thio-metallates in general and of MoS_4^{2-} in particular.

A number of [Fe-M-S] (Mo, W) complexes have been synthesized in recent years as possible models for the molybdenum site of the enzyme nitrogenase. These model complexes can be classified into two categories.

i) the cubane model, and

ii) the linear model.

In all the model complexes synthesized todate, $[MoS_4]^{2-}$ has been used as a molybdenum source, since $[MoS_4]^{2-}$ is unique in providing a soluble, reactive source of molybdenum and sulfur which can form complexes with iron salts. The analogous tungsten compounds have also been prepared for a comparative study. Despite the plethora of new inorganic compounds of molybdenum and tungsten, relatively few studies have been reported on reactivity towards organic reagents. The first systematic investigation of such reactivity was started by Stiefel and coworkers[59] in the study of reactions of alkynes with Mo-S system.

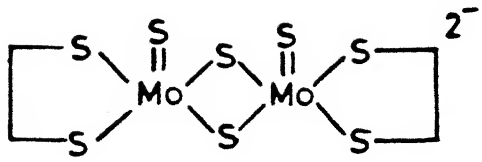
Known reactions of alkynes with S-ligand complexes are of two types:

(i) In the first or classical type the alkyne adds directly to the metal to form either π bound[60a-c] or σ bound[60d] complexes.

(ii) In the second type the alkyne reacts with sulfide, disulfide or polysulfide ligands to form 1,2-dithiolene ligand.[61]

Stiefel and coworkers chose the dianion $[Mo_2S_2(\mu\text{-}S)_2(SCH_2CH_2S)_2]^{2-}$ **1**, whose structure contains a syn-$Mo_2S_4^{2+}$ core,[62] as the starting material for their studies. When tetraethyl ammonium salt of **1** was treated with two or more equivalents of dimethylacetylene dicarboxylate (DMAC), 2 equivalents of ethylene were liberated. Apparently, in the major reaction the activated acetylene attacks the 1,2-ethane dithiolate ligands to displace ethylene[63] rather than adding to the syn-$Mo_2S_4^{2+}$ core by a process analogous to that observed for the anti-$Mo_2S_4^{2+}$ core in $(Me_nCp_2)Mo_2S_2(\mu\text{-}S)_2$ (n = 1, 5) complexes.[61] However, when they treated the well known anion $[Mo_2O_2(\mu\text{-}S)_2(S)_2]^{2-}$ **2**, instead of the expected addition of dimethylacetylenedicarboxylate (DMAC) to occur at the terminal S_2^{2-} ligands to yield 1,2-dithiolene complex (**2** → **3**), they obtained $[Mo_2O_2(\mu\text{-}S)_2(S)_2.2DMAC]^{2-}$ **4** (Scheme 1.1). Here the acetylenes have inserted into the Mo-S bonds of the terminal disulfides (rather than into S-S bonds) to form novel five membered metalla-2,3-dithiacyclo-pent-4-ene rings. The factors

Scheme-1.1

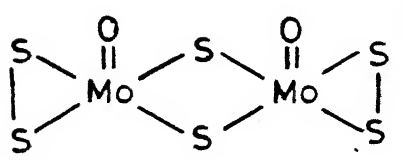


1

+ $2H_3C\,CO_2C \equiv C\,CO_2CH_3$

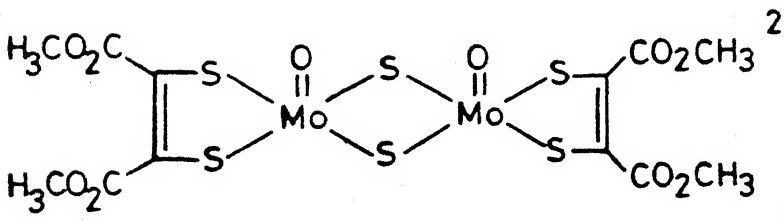
$\downarrow$

$2CH_2=CH_2$

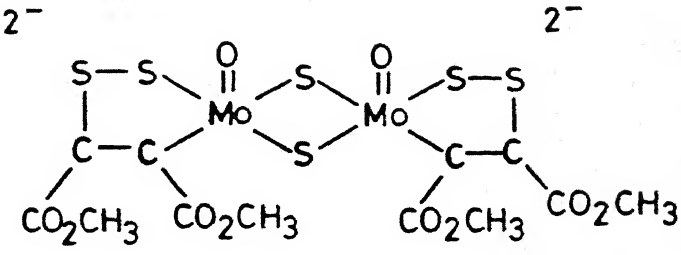


2

+ $2H_3C\,CO_2C \equiv C\,CO_2CH_3$

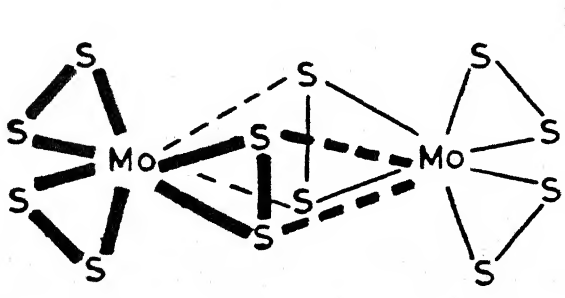


3



4

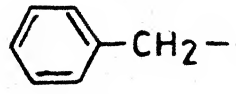
Scheme-1.2



5

+ R–Br $\longrightarrow$ R–S–R + R–S–S–R

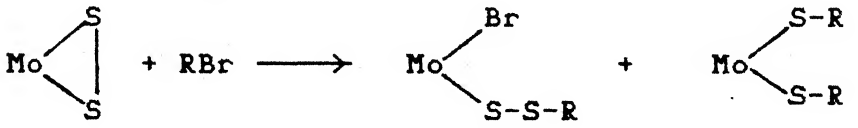
8b 8

Where R = 

that lead to such insertion rather than 1,2-dithiolene formation or direct coordination to molybdenum are not yet understood.

Harpp and MacDonald[64] recently reported their initial findings on reaction of a molybdenum-persulfide complex $(NH_4)_2[Mo_2S_{12}]^{2-}$ **5** with benzyl bromide **7b**. The reaction was carried out in benzene in a sealed tube at 90 °C to give a mixture of sulfide **8b** and disulfide **8** (**Scheme 1.2**).

The following mechanism was proposed for the alkylation reaction:



$$\xrightarrow{RBr} \underset{\mathbf{8}}{RSSR} + \underset{\mathbf{8b}}{RSR}\ .$$

1.1b DISULFIDES

The chemistry of tetrathiotungstates and tetrathiomolybdates, discussed in this chapter and later on, deals with the synthesis of disulfides to a large extent. Hence, it is appropriate that a brief introduction on the nature and importance of the disulfide linkage and the variety of methods available for the synthesis of disulfides is presented so as to put the present work in the right perspective.

Materials containing the disulfide functional group are encountered in diverse places throughout nature and commerce. The sulfur-sulfur bond in compounds imparts many properties most of which are based on its role as a cross linking site. Thus, in wool[65] the disulfide bonds serve as the cross links for the main polypeptide chains, and these cross links impart the desirable properties that differentiate wool from other protein fibers.

Similarly, the production of the synthetic polycaprolactam fiber nylon-6 involves the chemical control of the number and type of cross links, one of which is the disulfide cross link, in order to obtain the desired properties of crimping and helical coiling.[66]

The hair waving industry[67] is mostly concerned with the rupture and reformation of the disulfide bond. Human hair, a keratin, is quite similar to wool in that both contain a

fraction of the disulfide cross links that is resistant to cleavage by various disulfide specific reagents. These resistant disulfide links maintain the protein skeletal structure of the hair and prevent complete loss of its fiber properties. The objective is to cleave just enough disulfide bonds of the non-resistant, non-skeletally important type so as to make hair sufficiently pliable to assume the shape desired.

In proteins, the disulfide cross link may be intrachain (e.g. bovine ribonuclease) or interchain (e.g. insulin).[68] In addition to this structural role, there is evidence that disulfide bonds take part in some enzyme and harmone reactions.[68] Peter[69] showed that the disulfide linkages in the enzyme trypsin, chymotrypsin and chymotripsinogen must be retained in order to preserve their activity. In ribonucleases, activity is still high after two of its disulfide cross links per mole have been reduced but is completely lost on reduction of all four.[70]

Alkyl disulfides have been recommended for extracting oxygenated compounds from aqueous solutions in the Fischer-Tropsch process.[71] Some have been used in cutting oils.[72] In lubricating oils, various disulfides have been claimed to improve film strength[73] and detergent action,[74] to prevent sludge formation,[75] inhibit corrosion,[76] stabilize and serve as antioxidants.[77] Propyl disulfide is a stabilizer for pure hydrocarbons.[78]Butyl, i-amyl and methyl phenyl disulfides stabilize petroleum wax.[79] Several aromatic disulfides are

stabilizers for photographic emulsions.[80] Allyl disulfide prevents damage to films by heat and light.[81]

Disulfides are antagonistic to lead tetraethyl.[82] Injected into engine fuels they are claimed to prevent carbonization of metal parts.[83] Their addition to diesel fuels has been suggested,[84] but their use is limited on account of corrosion. Certain disulfides are claimed as flotation agents.[85]

Disulfides have been used as constituents of resins.[86] They serve as regulators in emulsion polymerization,[87] various disulfides have been suggested as solvents,[88] reclaiming agents,[89] softners,[90] plasticizers[91] and modifiers[92] for different kinds of rubbers. They act as vulcanization accelerators[93] but are less active than the corresponding mercaptans.

The disulfides from petroleum distillates have been claimed as pesticides.[94] Methyl disulfide is effective against nematode larvae[95] and methylallyl against blow flies.[96] Aryl disulfides are recommended for use in fly sprays,[97] in tree sprays[98] and for dusting wheat to destroy rust.[99]

Several monocyclic disulfides occur naturally. Derivatives of 1,2-dithiolane include the alkaloid brugine,[100] the neurotoxic compound nereistoxin from marine worm,[101] the acid from asparagus,[101] charatoxin from the green fresh water alga Chara globularis,[101] α-lipoic acid[102] and the newly discovered Guinesine-A, B and C.[103]

The various methods by which disulfides can be prepared are:

(1) BY OXIDATION OF THIOLS

A number of oxidants are known to convert mercaptans to disulfides. Among these oxidants oxygen, hydrogen peroxide, lead oxide, copper sulfate, hypohalides and iron(III) salts are usually recommended for preparative use.[104] Although nitrous oxide, sulfuryl chloride, chromium and selenium compounds, peracids and their salts, sodium polysulfide, sulfur dioxide, elemental sulfur are known to bring about the above transformation, they are less commonly used. Less selective oxidants are nitric acid, bromine, chlorine, sulfuric acid and potassium permanganate

The oxidation of a pure mercaptan by air is extremely slow, if at all, but in the presence of a catalyst it may be rapid. The oxidation of a mercaptan to the disulfide may be effected by passing its vapor with air over a catalyst, such as bauxite,[105a] iron,[105b,c] copper or other metals,[105b] or an alumina base catalyst.[105d] Activated charcoal at 100°C, or above has been recommended.[105e,f]

In alkaline solution, mercaptans are oxidized by gaseous oxygen.[106a] This oxidation can be speeded up by catalysts.[106b] The metals that aid the alkaline oxidation, arranged in order, are: aresenic, copper, antimony, zinc, cadmium, silver, iron and nickel.[106c] The oxidation is aided by supplying the oxygen

under pressure.[106d]

The simplest method of preparing a disulfide from a mercaptan is by an exchange reaction as shown in Eqn. 1.3.

$$CH_3CH_2CH_2S\rightarrow_2 \; + \; 2\; CH_3(CH_2)_8CH_2SH \rightleftharpoons 2\; CH_3CH_2CH_2SH + CH_3(CH_2)_9S)_2 \quad .. (1.3)$$

This reaction is brought about by heating[107a] or in the presence of catalysts.[107b]

In the presence of alkali ammonia or an amine, sulfur (or sodium disulfide) converts a mercaptan to disulfide.[108] (Eqns. 1.4 and 1.5).

$$2\; RSNa + S \longrightarrow RSSR + Na_2S \quad .. (1.4)$$

$$2\; RSNa + Na_2S_2 \longrightarrow RSSR + 2\; Na_2S \quad .. (1.5)$$

Iodine oxidizes thiols stoichiometrically. It is not only one of the best but also one of the most convenient methods of determining thiols as well (or disulfides, after reduction with zinc and acetic acid).[109a] Sodium or lead salts can also be oxidized[109b] (Eqn. 1.6)

$$2\ RSH + I_2 \longrightarrow RSSR + 2\ HI \qquad .. (1.6)$$

Bromine in dry carbon tetrachloride converts a mercaptan to disulfide rapidly.[110]

Mercaptans are oxidized to disulfides by ferric compounds. Use of ferric chloride in ether is convenient and mild; for example, it works well with a hindered arene thiol[111a] and is the reagent of choice for cyclizing 1,5-pentanedithiol.[111b] Potassium ferricyanide, also mild, was used to synthesize oxytocin.[111c] Catalytic oxidation of thiols to disulfides can be effected using $[Fe_4S_4(SR)_4]^{2-}$ cluster.[111d]

A variety of other compounds effect the oxidation of mercaptans: chromates,[112a-d] oxides of chromium,[112e,f] selenium dioxide,[113a,b] selenium tetrachloride,[113c] chloropicrin,[114a] diazonium compound,[114b] various salts,[115a] nitrosyl chloride[115b] and lead tetraacetate.[116]

(2) FORMATION OF DISULFIDES BY REDUCTION

Reduction often provides convenient routes to disulfides for e.g., reduction of any arene sulfonyl chloride to its disulfide by HI is probable if the substituents present on the aromatic ring resist HI.[117] Reduction also occurs with HBr which thus might be an alternative if R of Eqn. 1.7 contains groups incompatible with HI and to prevent bromination of the disulfide, bromine is scavenged by agents like Na_2SO_3 or

aniline.[118] Alkane sulfonate salts can be reduced to disulfide with PBr_3-PBr_5 in 26-87% yield.[119]

$$2\ RSO_2Cl \xrightarrow{\substack{HI,\ HBr,\ Mo(CO)_6,\ Cl_3SiH\text{-}Pr_3N,\\ (RO)_3P,\ R_3P,\ Me_3SiCl/NaI,\ AlI_3}} RSSR \qquad .. (1.7)$$

Both arene and alkane sulfonyl chlorides are reduced to disulfides by hexacarbonyl molybdenum in dry tetramethyl urea.[120]

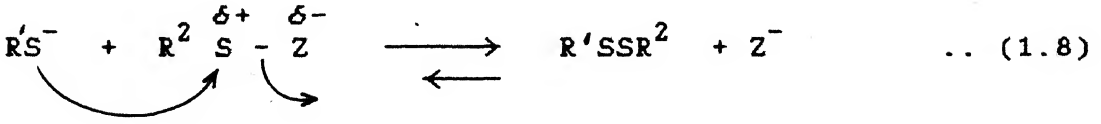
An arenesulfonyl chloride (but not an ester) is reduced by trichlorosilane in benzene with amine catalysis (Eqn. 1.7), as are sulfinyl and sulfenyl chlorides or their esters (53-91%); the mechanism is still unclear.[121] Sulfonic acids and sulfonyl derivatives are reduced to the corresponding disulfides with iodide in the presence of boron halides.[122] Sulfonyl halides and derivatives are also reduced to the disulfide by iodotrimethylsilane.[123] Aluminium iodide is also known to effect this transformation.[124]

Phosphite esters reduce arene sulfonyl chloride, arene sulfenyl chlorides or thiol sulfonates to disulfides along with other products.[125] Phosphines reduce arene sulfonyl chlorides to disulfides as well as to thiols and sulfinic acid. Phosphines also reduce α disulfones, thiolsulfonates or polysulfides to disulfides.[125] However, care is necessary because phosphites and phosphines can desulfurize disulfides to

monosulfides.[125]

(3) FORMATION OF DISULFIDES BY THIOALKYLATION OF THIOLS

Foss in 1947 first recognised that many diverse classes show the "sulfenyl" behavior represented for RSZ in Eqn. 1.8, that one expects from sulfenyl chlorides.[126] Thioalkylation of a thiol by sulfenyl derivative gives unsymmetrical disulfides.

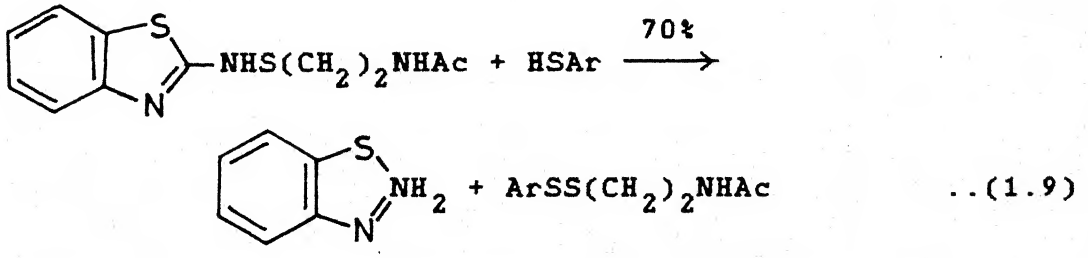


$$R'S^- + R^2S^{\delta+}-Z^{\delta-} \rightleftharpoons R'SSR^2 + Z^- \qquad .. (1.8)$$

Among the groups Z that can be displaced by thiolate ion are: R_2N^-, halide ion, SCN^-, RSO_2^-, $ROC(O)S^-$, SO_3^{2-}, RS^- and CN^-.

(i) With Sulfenamides

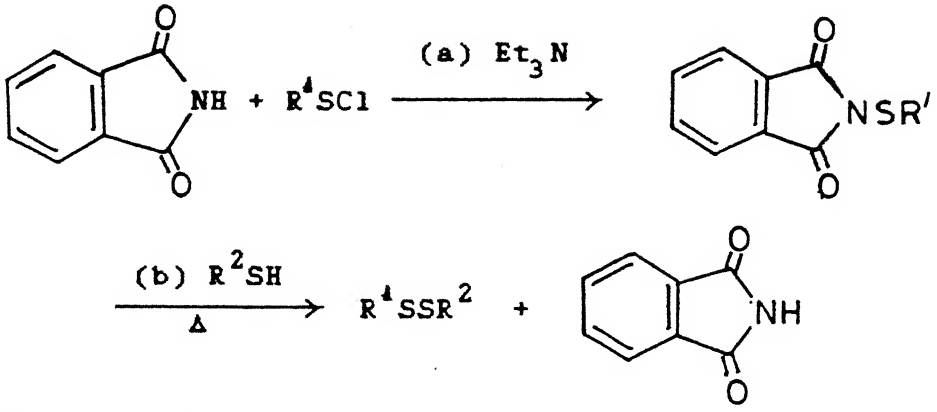
The following equation illustrates the thioalkylation of a thiol by a sulfenamide[127] (Eqn. 1.9). Several syntheses of unsymmetrical disulfides have been achieved by ingenious use of sulfenamides.



$$\text{benzothiazole-NHS}(CH_2)_2NHAc + HSAr \xrightarrow{70\%} \text{2-aminobenzothiazole} + ArSS(CH_2)_2NHAc \qquad ..(1.9)$$

Two reports appeared simultaneously that made use of

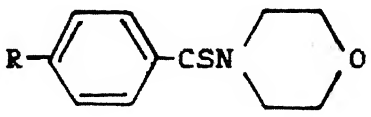
sulfenylphthalimides[128,129] as shown in the equation (Eqn. 1.10):



..(1.10)

Sulfenyl succinimides or maleimides have also been used.[130] Precipitation of the imide drives the reaction to completion, and the disulfide is readily recovered from the solution. Advantage of this method is the easy preparation and unlimited shelf-life of the precursor sulfenylphthalimides.[130]

Okecha has reported[131] that the thioamides I (R = -H, -OMe, -Cl, -Br) are reduced to the corresponding $(p\text{-}RC_6H_5CH_2S)_2$ in 30-40% yield on treatment with $NaBH_4(Me_2CHOH)$.



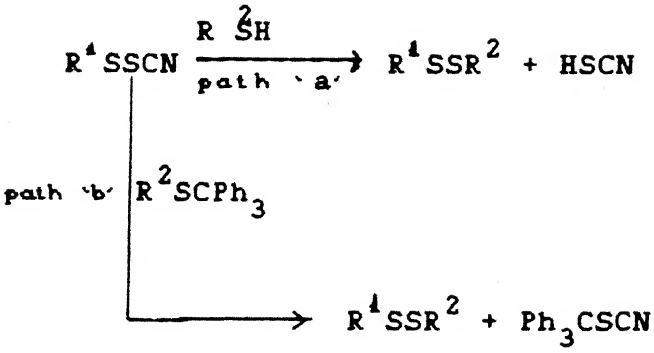
I

Disulfides were not obtained on similar treatment of $RCSNR_2$ (R = aryl, R^1 = Me, $R^{2'}$ = piperidino, R = alkyl, R_2' = morpholino). The selective reduction of I by $NaBH_4$ is probably due to electronic and steric factors.

(ii) <u>With Sulfenylthiocyanates</u>

Thioalkylation of a thiol can be achieved as shown in the

following equation (Eqn. 1.11):

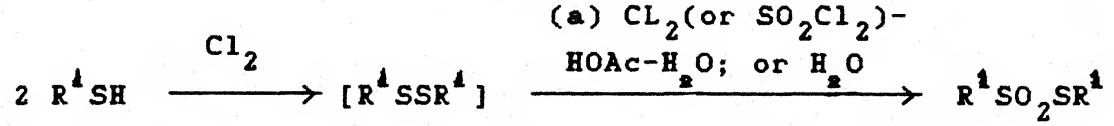


.(1.11)

The power and flexibility of the sulfenyl thiocyanate route were enhanced greatly by the findings that the reaction succeeds even when the hydrogen of the thiol is replaced by a trityl, benzhydryl, α-pyranyl or isobutoxy methyl group. Variation like that shown in Eqn. 1.11 (path 'b')thus became possible.[132] Advantages of such routes are high reactivity of thiols and certain thioethers towards thiocyanogen and sulfenyl thiocyanates.[129] Hiskey and his associates have used this method extensively for the synthesis of aliphatic disulfides and for sulfur containing polypeptides.[133,134]

(iii) <u>With Thiolsulfonates $R^1SO_2SR^2$ and Thiolsulfinates R^1SOSR^2</u>

Synthesis of disulfides by use of thiolsulfonates is shown in the following equation (1.12):



$$\xrightarrow{\text{(b) } R^2SNa} R^1SSR^2 + R^1SO_2Na \qquad ..(1.12)$$

The chief advantage of this route (like that with sulfenamides) is that reagent desired for thioalkylating several thiols,can be prepared once and kept indefinitely. A disadvantage, with a symmetrical thiolsulfonate is that half of it is wasted as the displaced sulfinate (Eqn. 1.12).

A symmetrical aliphatic thiolsulfonate can be obtained (87%) smoothly by the Douglas-Farah reaction in which one carefully chlorinates a disulfide at -10° in acetic acid and then adds water. Unsymmetrical thiolsulfonates may be made by a modified route (82-84%).[135] Aromatic thiol sulfonates can be prepared similarly from a disulfide or thiol (75-89%).[136]

Thiolsulfinates can be prepared from disulfides and used to convert thiols to unsymmetrical disulfides all in one operation[137] (Eqn. 1.13):

$$2\ R^1SH \xrightarrow{H_2O_2} R^1SSR^1 \xrightarrow{RCO_3H} R^1S(O)SR^1 \xrightarrow{2R^2SH} 2\ R^1SSR^2 + H_2O \qquad ..(1.13)$$

(iv) <u>With Sulfenyl thiolcarbonates ($R^1SSCO_2R^2$)</u>

In this elegant route,[138] one first obtains carboalkoxy sulfenyl chloride[139] in two steps which is then converted to a sulfenyl thiol carbonate (Eqn. 1.14):

$$Cl_3CSCl \xrightarrow{H_2O,\ H_2SO_4} ClSC(O)Cl$$

$$\xrightarrow{ROH} ClSCO_2R \xrightarrow[0\ ^{\circ}C]{R^1SH} R^1SSCO_2R \qquad .. (1.14)$$

$$RO\text{-}\overset{\overset{O}{\|}}{C}\text{-}S\text{-}S(R^1) + SR^2(H) \xrightarrow{25\ ^{\circ}C} R^1SSR^2 + COS + ROH \qquad .. (1.15)$$

Sulfenylthiol carbonate is then fragmented in a heterolytic fashion by a second thiol to give the corresponding disulfide[140] (93-99%) (Eqn. 1.15).

(v) With Bunte Salts ($RSSO_3^-$)

Disulfides can be prepared indirectly by the reaction of Bunte salts with acid solution of iodide, thiocyanate ion or thiourea,[141] by pyrolysis or treatment with hydrogen peroxide.

$$R^1SSO_3^- + R^2S^- \rightleftharpoons R^1SSR^2 + SO_3^{2-} \qquad .. (1.16)$$

Best results ensue with short reaction periods at 0 $^{\circ}C$ maintaining the pH around 8. In this reaction, the disproportionation may be troublesome and fails to produce disulfide in high yields (10~40%).[141] Bunte salts also have been used to prepare tri and tetra but not pentasulfides.[142]

(vi) With Thiocyanates (RSCN)

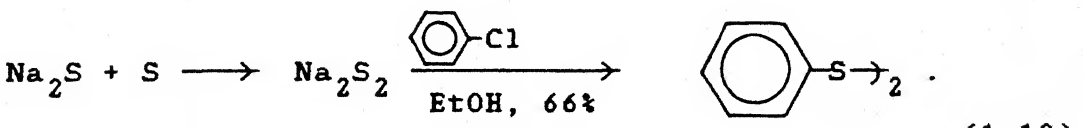
This method apparently has been used to make mostly symmetrical disulfides.[143] It is rarely used now, although it proved reasonably effective for converting metal 1-alkene thiolates to unsymmetrical disulfides[144] (Eqn. 1.17):

$$R^1SCN + R^2SH \longrightarrow R^1SSR^2 + HCN \quad .. (1.17)$$

Disulfide results when a thiocyanate is heated with a base, perhaps because thiolate ion is generated and then is either thioalkylated by the thiocyanate or oxidized.

(4) BY OTHER METHODS

Arylation of Na_2S_2 with a suitably activated aryl halide can afford a good synthesis of a symmetrical disulfide[145] (Eqn. 1.18). Arene diazonium salts also arylate Na_2S_2, but one should be aware of the possible explosions, presumably caused by accumulation of diazosulfides.[143,146] Since "Na_2S_2" is a statistical compound, sulfides, trisulfides and higher sulfides are also formed.



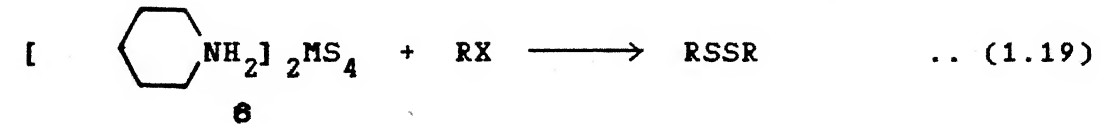
.. (1.18)

1.2 RESULTS AND DISCUSSION

Very little is known on the use of thiometallates in organic chemistry even though they have been the subject of study by theoretical and inorganic chemists for quite some time.[1] The only reaction of significance that has been reported in the chemistry of thiometallates of molybdenum or tungsten with organic reagents is the interesting alkylation of a persulfido complex of molybdenum, $Mo_2S_{12}^{2-}$ **5** with benzyl bromide **7b**. Harpp and MacDonald found that reaction of $(NH_4)_2$-Mo_2S_{12}, **5** with benzyl bromide **7b** in benzene in a sealed tube at 90 °C gave after work-up a 8:1 mixture of dibenzyl sulfide **8b** and dibenzyl disulfide **8** (**Scheme 1.2**). As can be seen, this molybdenum persulfide complex is not all that reactive and is also not selective since it produces a mixture of sulfides and disulfides from alkyl halides. Another disadvantage of this methodology is that the synthesis of the complex itself is tedious.[16a] Hence, it was decided to synthesize the more readily available simple thioanions of molybdenum and tungsten (MS_4^{2-}) and study the behavior of these metal-sulfur derivatives as sulfur transfer reagents in organic synthesis. We prepared the tetrathiotungstate **6a** and tetrathiomolybdate **6b** by following a modified procedure.[7,8] Piperidine, distilled water and tungstic acid were refluxed till the tungstic acid went into solution. H_2S was then passed into the solution at 60 °C for about 8 h. The resulting crystals were filtered and washed with isopropanol and ether and vacuum dried. They were stored

under dessicated conditions. The corresponding thiomolybdate **6b** was prepared by the same procedure using molybdic acid. The H_2S in this case was passed at ~28 °C for 0.5 h.

The tetrathiometallates **6a** and **6b** are soluble in dimethylformamide and to a lesser extent in acetonitrile and hence dimethylformamide was chosen as the solvent for all our reactions with **6a** and **6b**. Initial efforts were directed towards studying the behavior of tetrathiometallates **6a** and **6b** with alkyl halides including benzylic and allylic halides. Accordingly reaction of piperidinium tetrathiotungstate **6a** with alkyl halides in dimethylformamide at ~28 °C for 0.5-1.0 h gave after work-up the corresponding disulfides in good to excellent yields[147] (Eqn. 1.19).



$$[\ (C_5H_{10}NH_2)_2MS_4 \quad (\mathbf{6}) \quad + \quad RX \longrightarrow RSSR \qquad .. (1.19)$$

where **6a** = M = W

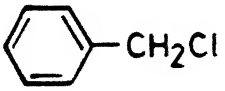
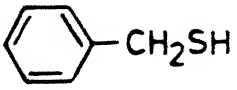
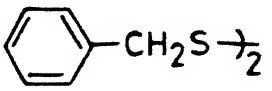
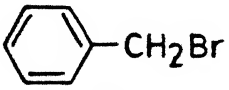
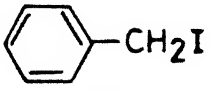
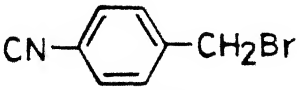
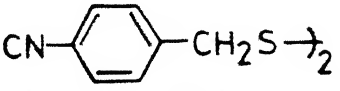
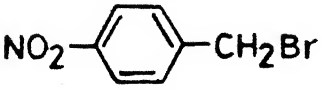
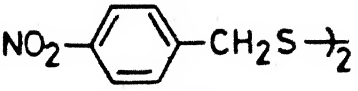
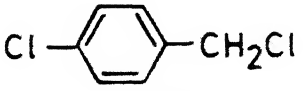
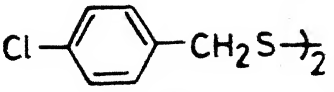
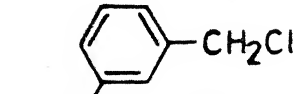
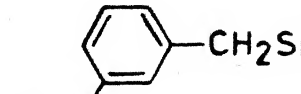
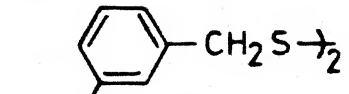
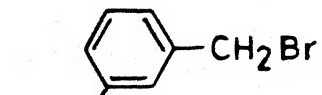
6b = M = Mo .

The results of the sulfur transfer reactions on a variety of alkyl halides with **6a** are summarized in **Table 1.1.**

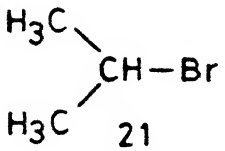
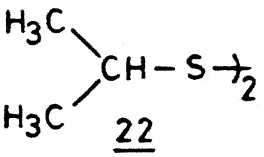
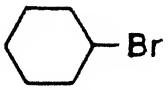
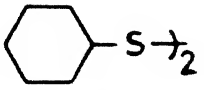
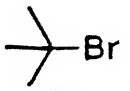
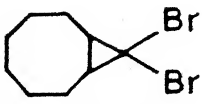
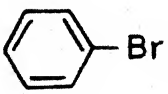
As the data in **Table 1.1** indicate, benzyl chloride **7a** gave a slightly higher proportion of the minor product, thiol **8a** (20%) compared to that obtained in the reaction of benzyl bromide **7b** with **6a** (17%). On the other hand benzyl iodide **7c** afforded the disulfide **8** as the only product in very high yield (98%). The reaction of benzyl iodide **7c** with **6a** is almost

TABLE 1.1

REACTION OF TETRATHIOTUNGSTATE 6a WITH ALKYL HALIDES

Entry	Substrate	Time (h)	Product (s)	Yield (%)
1	 7a	1.0	 8a	20
			 8	67
2	 7b	0.5	8a	17
			8	70
3	 7c	0.25	8	98
4	 9	0.1	 10	100
5	 11	0.1	 12	83
6	 13	0.5	 14	73
7	 15a	0.75	 16a	23
			 16	76
8	 15b	0.5	16a	17
			16	82

Contd --

Entry	Substrate	Time (h)	Product (s)	Yield (%)
9	$CH_3CH_2CH_2CH_2Br$ 17	3	$CH_3CH_2CH_2CH_2S\rightarrow_2$ 18	99
10	CH_3CH_2Br 19	0.5	$CH_3CH_2S\rightarrow_2$ 20	40
11	 21	5	 22	43
12	 23	12	 24	85
13	 25	0.1	 26	58
14	$CH_3CH_2CH_2CH_2OTs$ 27	13	18	63
15	 28	10	NO REACTION	
16	 29	10	NO REACTION	
17	 30	10	NO REACTION	

instantaneous whereas the reaction with benzyl chloride **7a** is slower. However, due to easy availability of starting materials, bromides were chosen as the substrates. Similar trend was observed with other substituted benzyl halides with yields ranging from 75-100%. p-Cyanobenzyl bromide **9**, p-nitrobenzyl bromide **11** and p-chlorobenzyl chloride **13** gave the correspond- ing disulfides **10**, **12** and **14** in 100, 83 and 73% yield, respectively. As expected, m-methoxybenzyl chloride **15a** gave a slightly higher proportion of the minor product, thiol **16a** (23%) compared to that obtained in the reaction of m-methoxybenzyl bromide **15b** with **6a** (17%).

This method is equally effective for forming aliphatic disulfides. Ethyl bromide **19** reacted with **6a** very rapidly (~0.5 h) to give the corresponding disulfide **20** in 40% yield. The low yield in the case of ethyl bromide is probably due to the high volatility of the starting material and the product. Butyl bromide **17** reacted with **6a** to give the corresponding disulfide **18** in 99% yield. The reaction took 3 h to go to completion. The reaction of butyltosylate **27** with **6a** was much slower (13 h) and gave the corresponding disulfide **18** in 63% yield. The two secondary bromides, isopropyl bromide **21** and cyclohexyl bromide **23** were much slower to react with **6a**. Isopropyl bromide **21** gave the disulfide **22** in 43% yield after 5 h whereas cyclohexyl bromide **23** gave the corresponding cyclohexyl disulfide **24** in 85% yield after 12 h. tert-Butyl-bromide **28** and 2,2-dibromobicyclo(6,1,0)nonane **29** were however, found to be inert to **6a** since starting materials could be

recovered unchanged after 24 h. Allyl bromide **25** reacted almost instantaneously (0.1 h) to give the corresponding disulfide **26** in 58% yield. Bromobenzene **30** did not react with **6a**.

In order to compare the reactivity of tetrathiotungstate **6a** with tetrathiomolybdate **6b**, we carried out the reaction of a number of alkyl halides with tetrathiomolybdate **6b**. The results are summarized in **Table 1.2**.

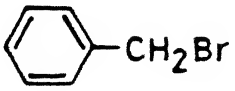
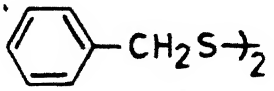
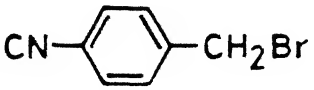
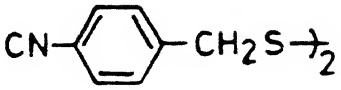
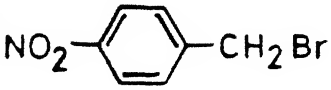
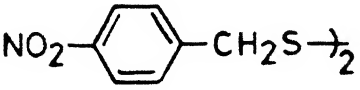
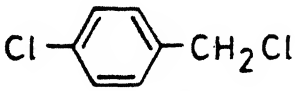
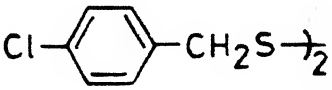
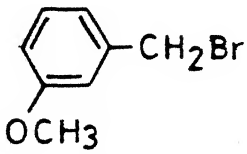
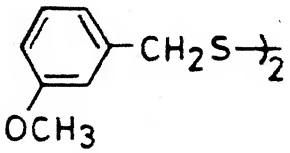
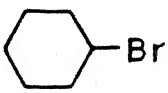
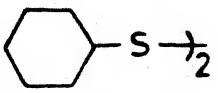
Tetrathiomolybdate **6b** reacts with alkyl halides to give the disulfides as the sole product. Benzyl bromide **7b** gave the disulfide **8** as the only product in 90% yield. p-Cyanobenzyl bromide **9** and p-nitrobenzyl bromide **11** gave the corresponding disulfides **10** and **12** in 65% and 59% yield, respectively, whereas p-chlorobenzyl chloride **13** gave the disulfide **14** in 99% yield. m-Methoxybenzyl bromide **15b** gave the disulfide **16** as the sole product in 73% yield. Butyl bromide **17** gave after 4 h 97% of the disulfide **18** whereas cyclohexyl bromide **23** gave the corresponding disulfide **24** in 76% yield after 12 h.

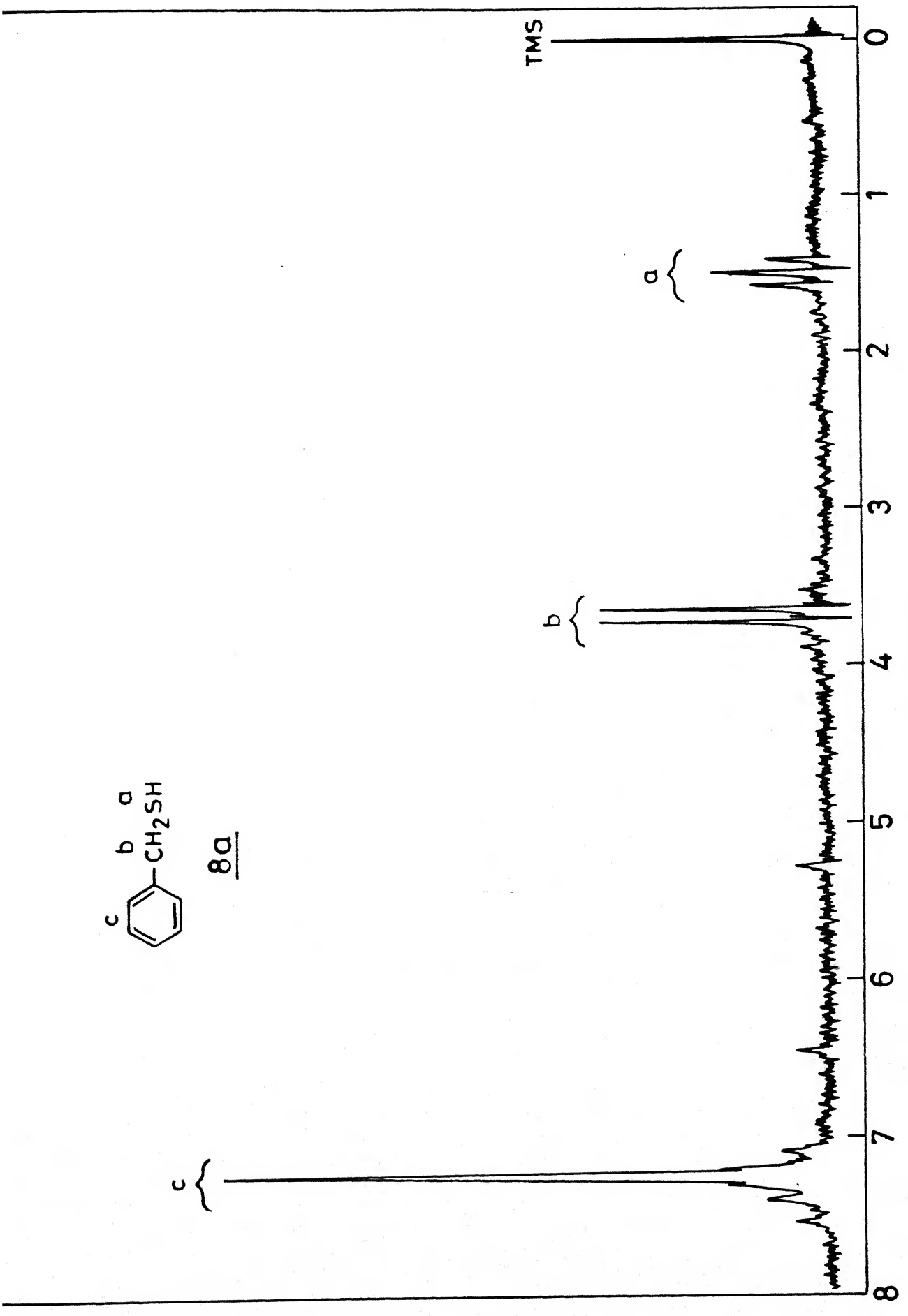
The tetrathiometallates **6a** and **6b** also react with alkyl tosylates to give the corresponding disulfides in excellent yields though the reaction of tosylates with **6** is much slower (12-15 h). The order of reactivity:alkyl iodide > alkyl bromide > alkyl chloride > alkyl tosylate is in line with the softness of the sulfur nucleophile. Aryl halides are not affected by **6a** or **6b** under the reaction conditions.

Although this is a good method for making symmetrical

TABLE 1.2

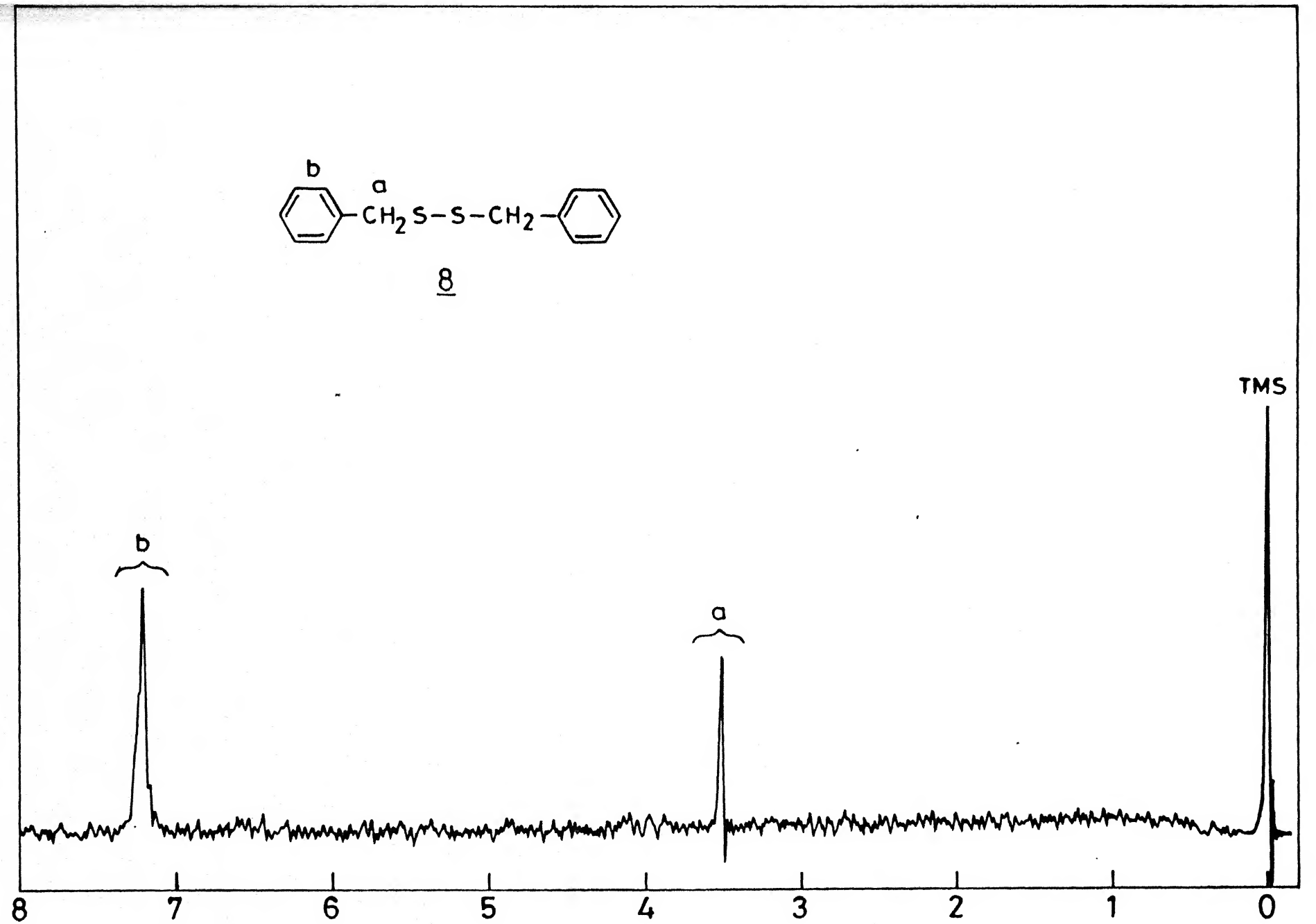
REACTION OF TETRATHIOMOLYBDATE 6b WITH ALKYL HALIDES

Entry	Substrate	Time (h)	Product	Yield (%)
1	 7b	0.5	 8	90
2	 9	0.1	 10	65
3	 11	0.1	 12	59
4	 13	0.5	 14	99
5	 15b	0.5	 16	73
6	$CH_3CH_2CH_2CH_2Br$ 17	4	$CH_3CH_2CH_2CH_2S\rightarrow_2$ 18	97
7	 23	12	 24	76

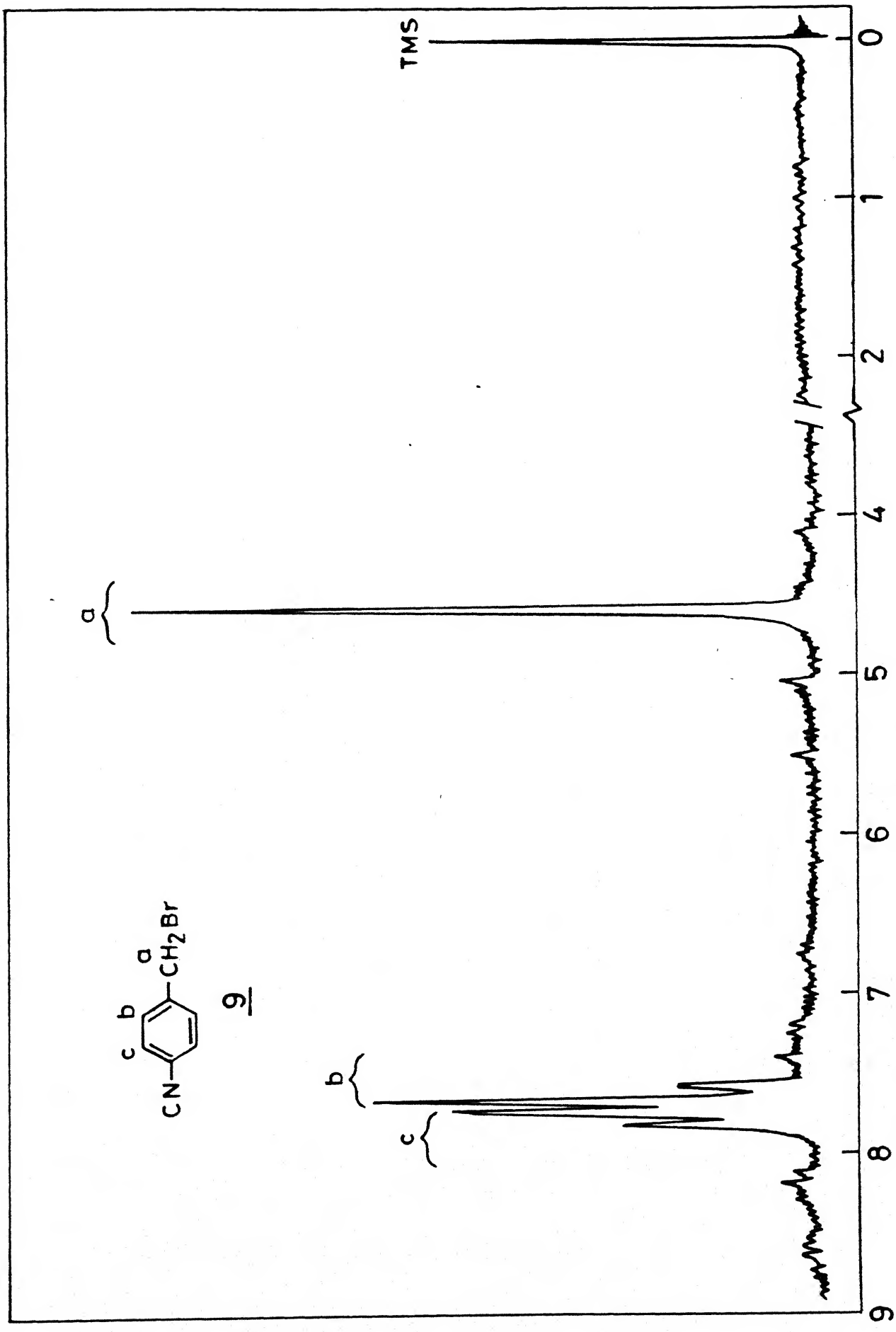


8a

^{1}H NMR spectrum (90 MHz) of 8a

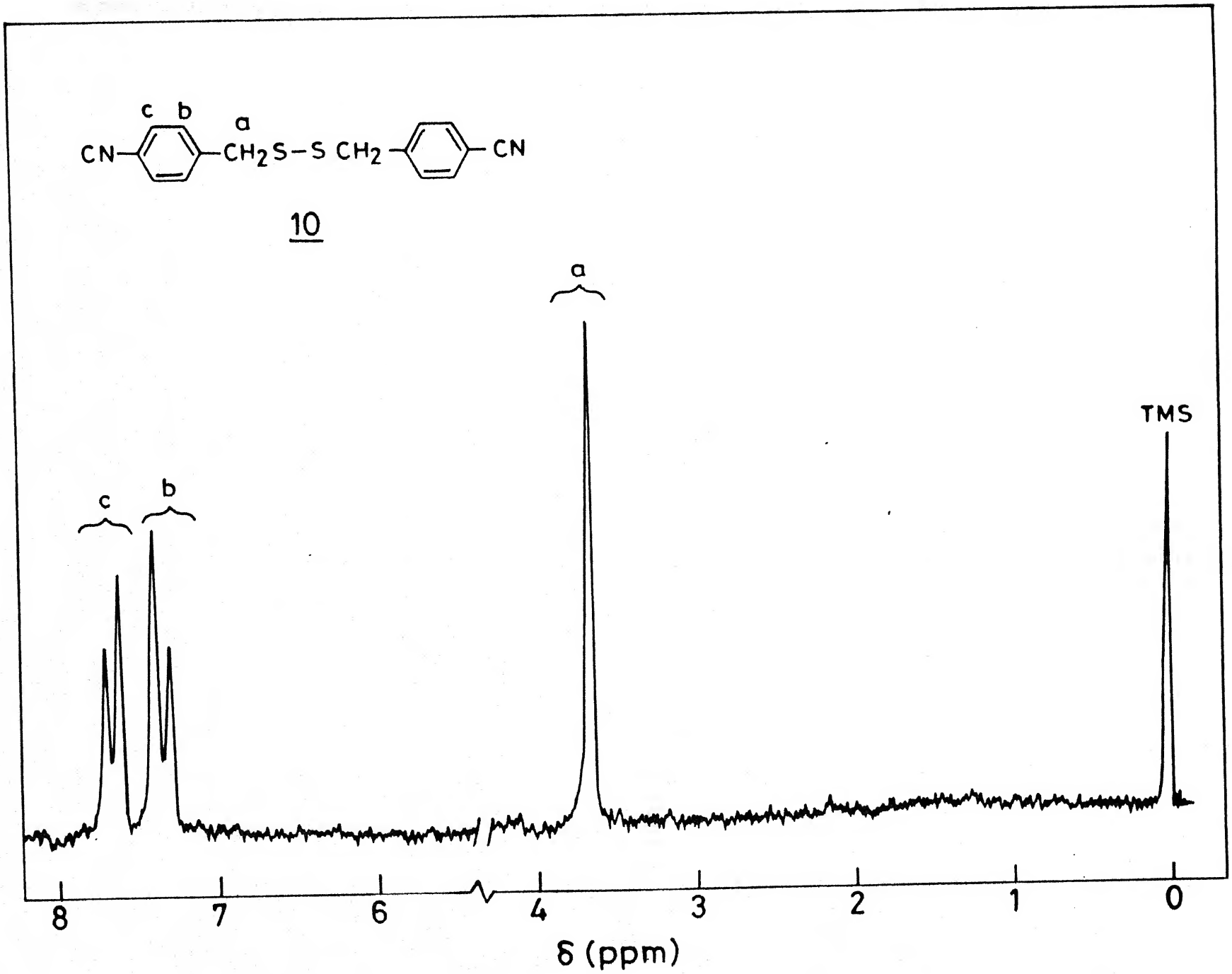


^{1}H NMR spectrum (90 MHz) of 8

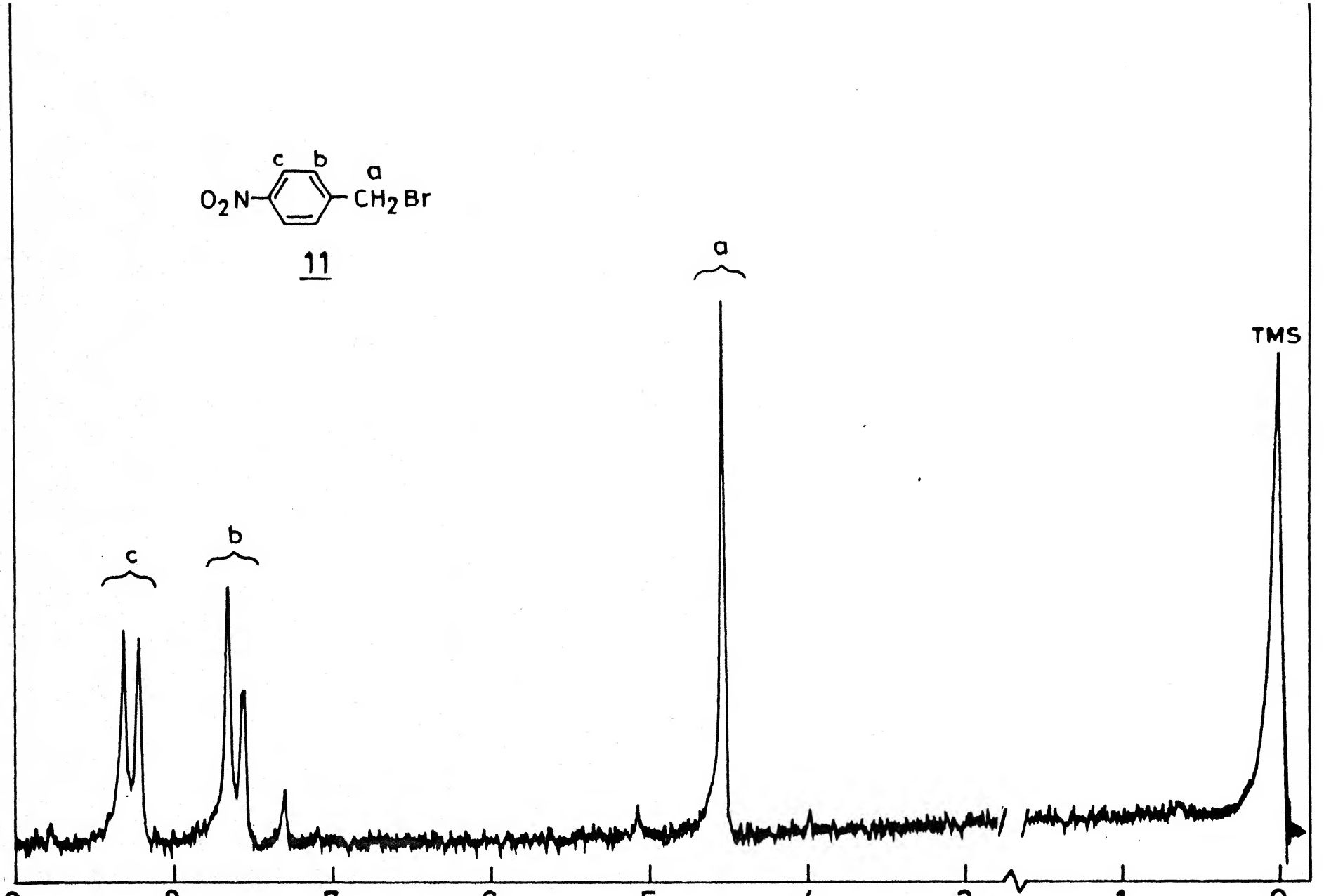


9

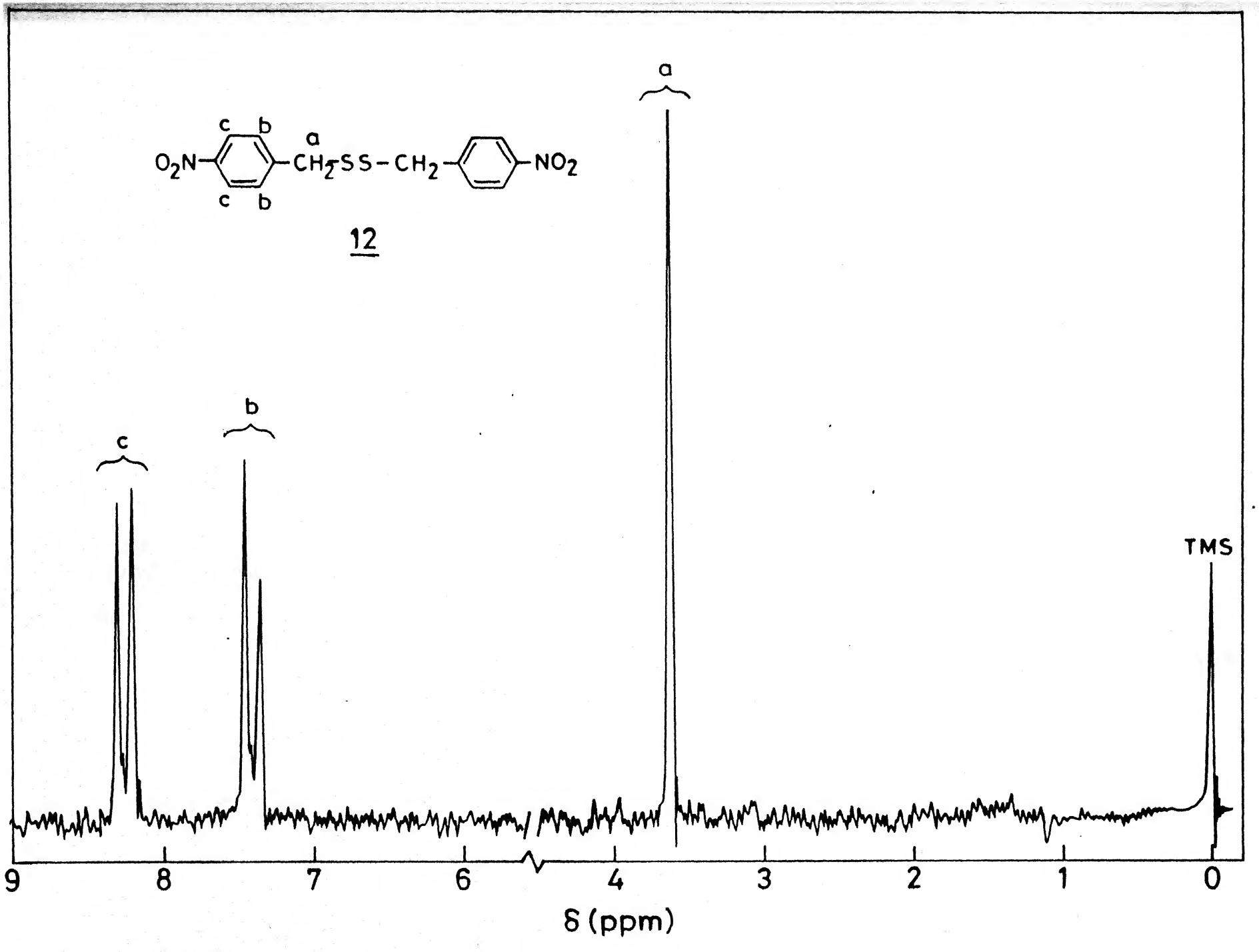
^{1}H NMR spectrum (90 MHz) of 9



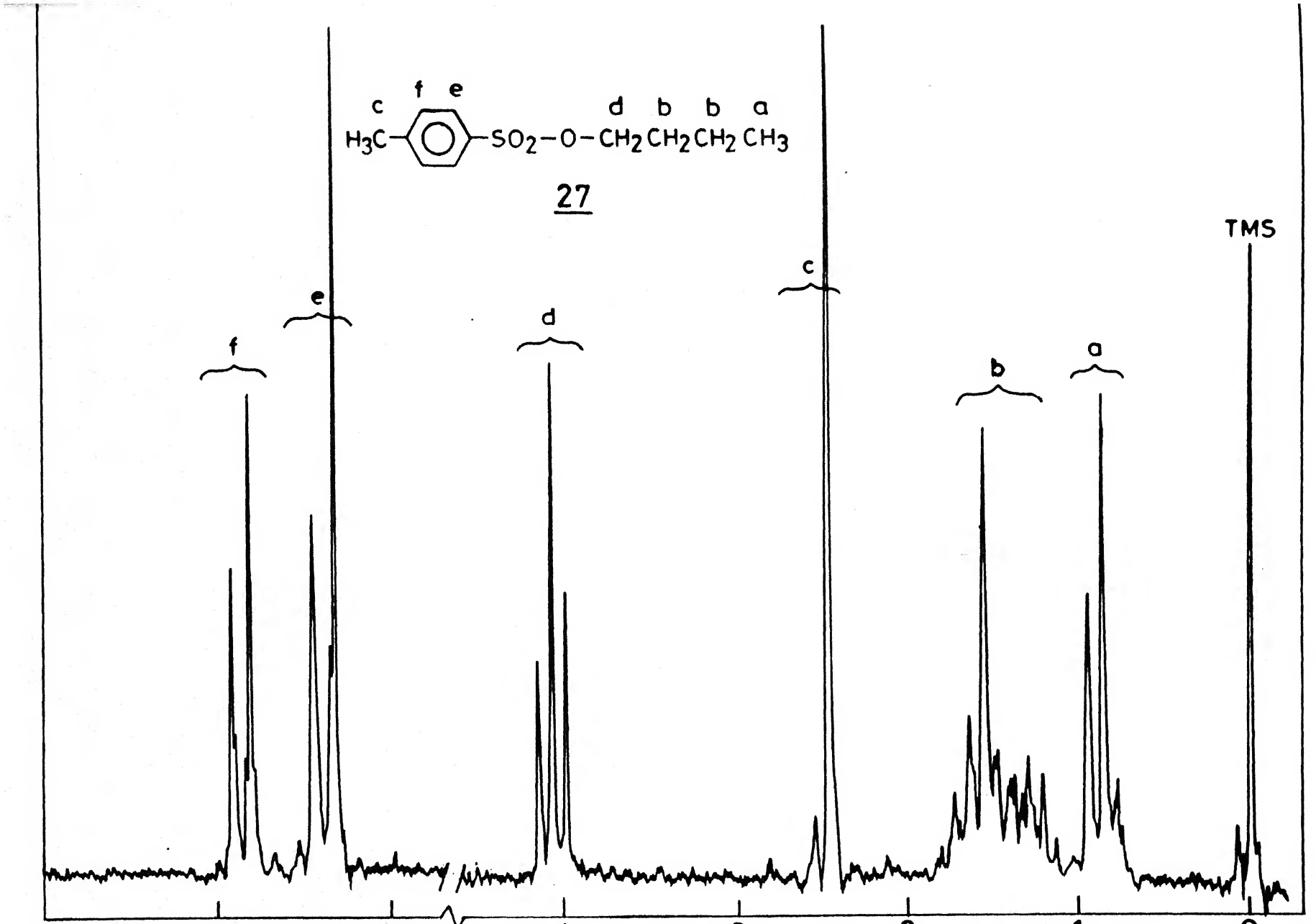
^{1}H NMR spectrum (90 MHz) of 10



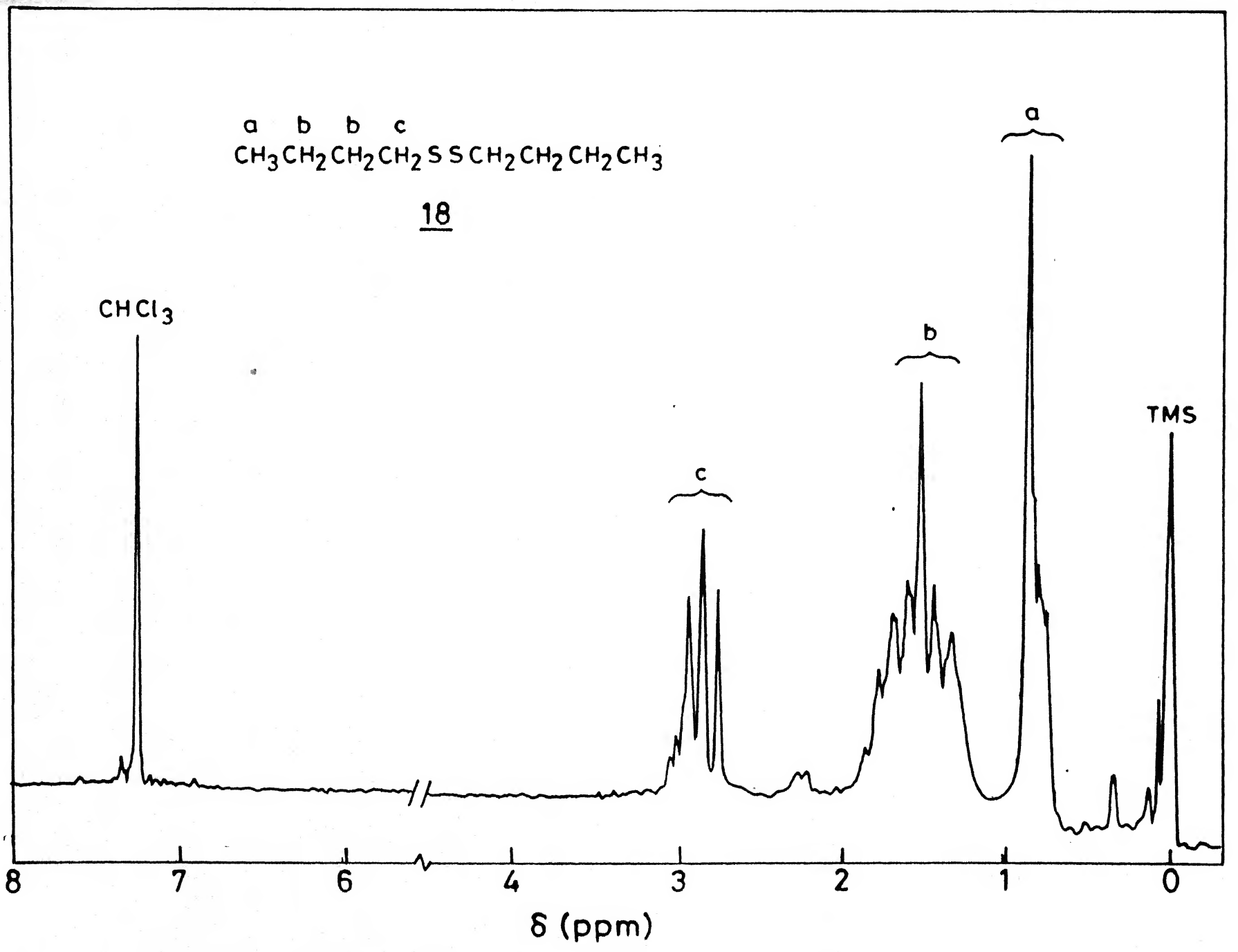
^{1}H NMR spectrum (90MHz) of 11



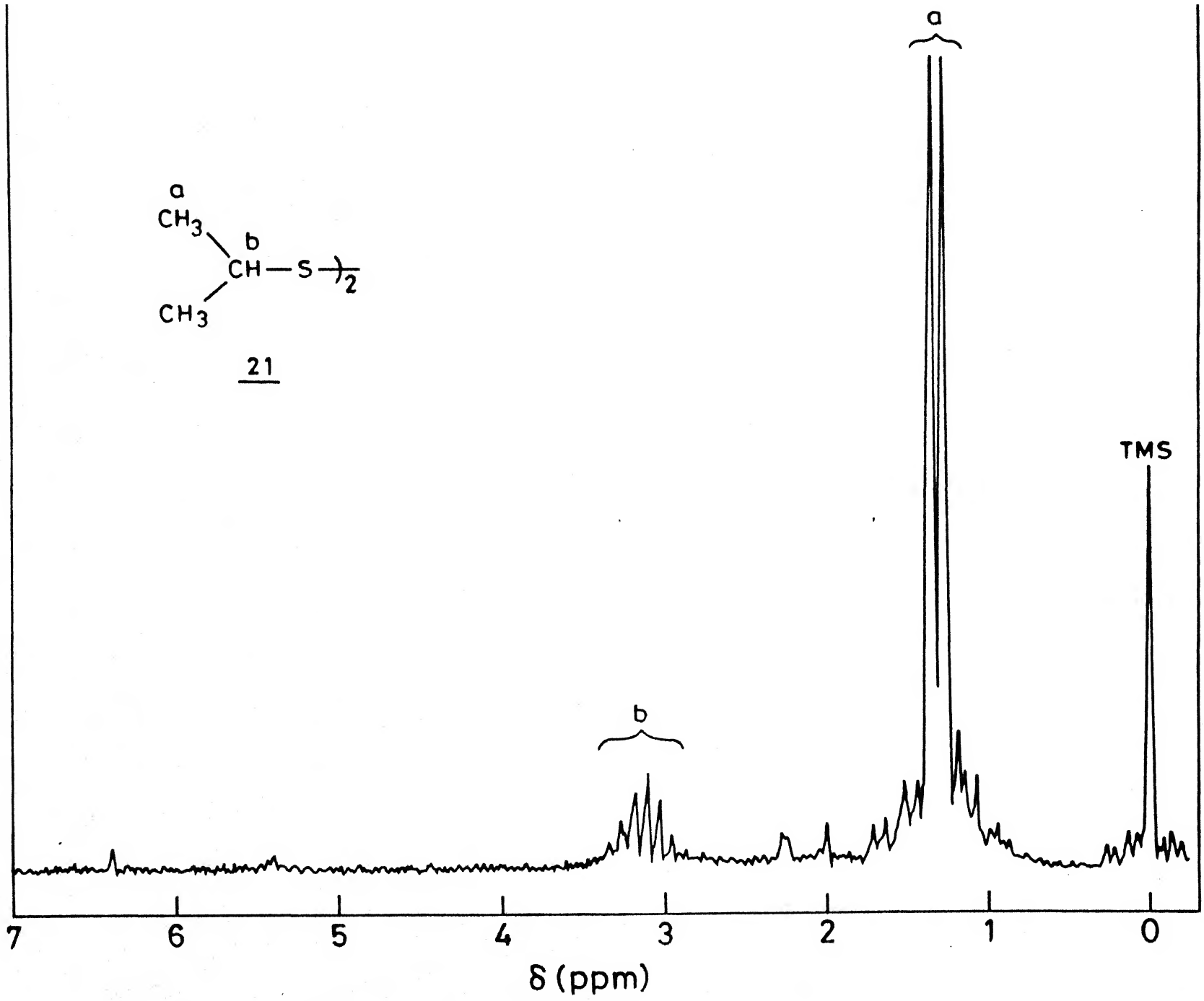
^{1}H NMR spectrum (90 MHz) of 12



^{1}H NMR spectrum (80 MHz) of 27



^{1}H NMR spectrum (80 MHz) of 18



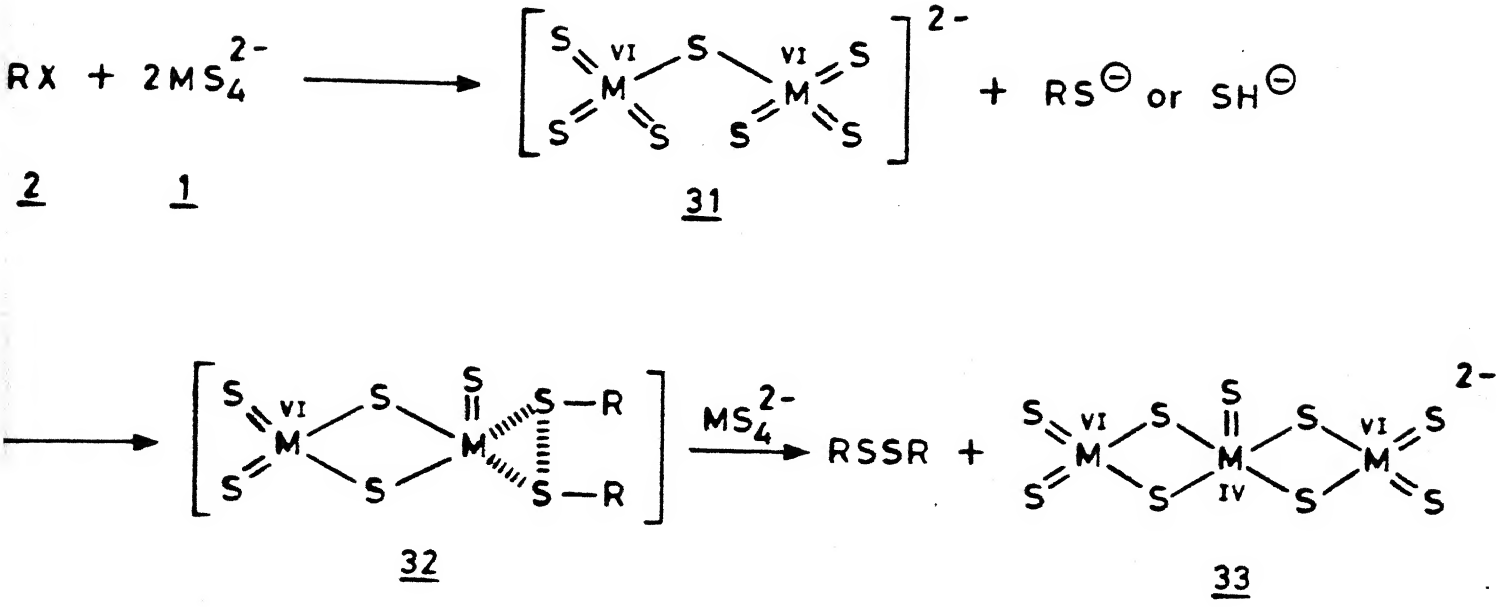
^{1}H NMR spectrum (90 MHz) of 21

disulfides, attempts to make unsymmetrical disulfides from two different alkyl halides result in a mixture of three compounds.

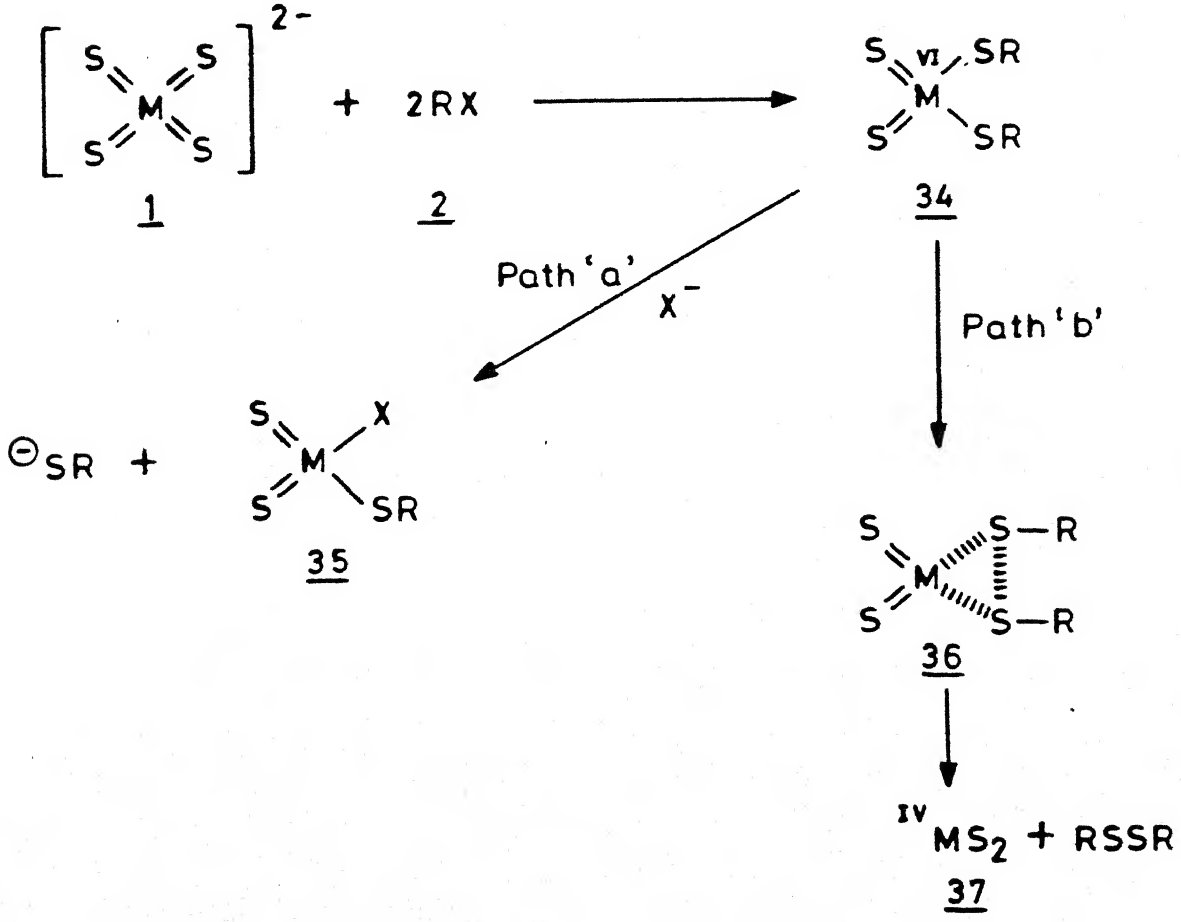
At the present time we do not have any direct evidence regarding the fate of the inorganic complex [Mo^{VI} or W^{VI}] after the reaction is completed. Attempts to purify, isolate and identify a single inorganic species from the reaction mixture, which incidentally can throw some light on the mechanistic pathway,have proved to be unsuccessful.We invariably end up with a dark gummy material which we believe is a mixture of more than one inorganic material, indicating that the reaction could be following more than one reaction pathway. Nevertheless, as a working hypothesis we propose a tentative mechanism for this novel alkylation which is outlined in **Scheme 1.3**.

The first step involves either an alkylation across the M-S bond to facilitate the departure of RS^- or protonation of WS_4^{2-} from piperidinium cation to help the departure of ^-SH resulting in the dimerization to form an intermediate $M_2S_7^{2-}$ ion **31**. This type of an ion has previously been postulated[32,148] and has been prepared by other routes in the literature. Although we cannot authenticate the inorganic product, the possibility of this ion being formed cannot be ruled out. Our speculation seems to be reasonable on the basis of the available literature data. $M_2S_7^{2-}$ **31** then undergoes reduction of the metal with the oxidation of the ligand in an induced intra- molecular electron transfer pathway to form the

Scheme 1.3



Scheme 1.4



disulfide. This suggestion is in support of an earlier observation that the alkylation of WS_4^{2-} bonds was the key feature of the mechanism of formation of $W_3S_9^{2-}$.[149] It is likely that the alkyl chlorides tend to yield thiols as a minor product as a consequence of the first step of the mechanism envisaged.[150]

Another tentative mechanism is outlined in **Scheme 1.4**. The first step envisages the alkylation across the M-S bond which then can be replaced by a ligand to facilitate the departure of RS^- (path a) which eventually gives rise to thiols. The alkylated product in an internal redox process (path b) can lead to the disulfide with the formation of MS_2 **37**.

The present methodology apart from being novel as a sulfur transfer reaction from thiometallates, compares favorably with other methods of synthesis of disulfides. Further work is necessary to conclusively delineate the mechanism of this reaction.

1.3 EXPERIMENTAL SECTION

Experimental Procedure

All the reactions were performed in oven dried apparatus. Reaction mixtures were stirred magnetically unless otherwise specified. Reaction product solutions were concentrated using a Perfit rotary evaporator and products were characterized by comparison with authentic samples (spectra, T.L.C., m.p.). Lassaigne's test was performed on each compound for detection of sulfur

Materials

Commercial grade solvents were distilled prior to use. Dimethyl formamide was initially purified by azeotropic distillation with benzene. The residual solvent was shaken with calcium oxide, filtered and distilled at reduced pressure. The fraction having b.p. 76 ^{o}C/39 mm Hg was collected. The distillate was stored over a type 4 Å molecular sieve.

Chromatography

Analytical thin layer chromatography was performed on Merck precoated glass backed silica gel 60F-254 0.25 mm plates. Visualization of the spots was effected by one or more of the following techniques:(a) ultraviolet illumination; (b) exposure to iodine vapour; (c) immersion of the plate in a 10% solution of phosphomolybdic acid in ethanol followed by heating to *ca.* 200 ^{o}C.

Column chromatography was performed using 60-120 and 100-200 mesh Acme silica gel. The flash chromatography was performed using Merck thin-layer chromatography silica gel.

Physical Data

Melting points (m.p.) were determined with a uni-melt capillary melting point apparatus and are uncorrected. Boiling points (b.p.) are uncorrected.

Bulb to bulb distillation was carried out on a Büchi-GKR-50 distillation unit.

Infrared (IR) spectra were recorded on Perkin-Elmer model 1320 and 580 spectrophotometers and are reported in wave numbers (cm^{-1}).

Proton magnetic resonance (PMR) spectra were recorded at 90 MHz on a Varian EM-390 instrument, at 80 MHz on Bruker WP-80 instrument and at 90 MHz on Jeol FX-90Q instrument. Chemical shifts are reported in parts per million down field from internal reference tetramethyl silane (TMS) (δ). Multiplicity is indicated using the following abbreviations : s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad); etc. Mass spectra (MS) were recorded on a Jeol JMS D-300 mass spectrometer. Principal molecular fragments are reported.

Preparation of Piperidinium tetrathiotungstate, **6a**[7]

Tungstic acid (5.0 g) was refluxed in a mixture of water

(10 ml) and piperidine (15 ml) for 1 h. The above solution was filtered and H_2S was bubbled rapidly at 60 °C for 8 h. The reaction mixture was cooled and the yellow crystals of **6a** formed were filtered, washed with isopropanol (50 ml) and ether (20 ml) and dried in vacuo (7.5 g, 78%).

IR (KBr): 3020, 2990, 2950, 1620, 1600, 1540, 1470, 1440, 1390, 1300, 1030, 1020, 990, 910, 655, 455 cm^{-1}.

$\lambda_{max}^{(CH_3OH)}$: 396 (11968).

Analysis: Calcd for $C_{10}H_{24}N_2S_4W$: C, 24.79; H, 4.45; N, 5.78.

Found: C, 24.58; H, 4.78; N, 5.72%.

Preparation of Piperidinium tetrathiomolybdate, **6b**[8]

Molybdic acid (5.0 g) was dissolved in a mixture of water (10 ml) and piperidine (15 ml). The solution was filtered and H_2S was passed rapidly into the solution at room temperature (28 °C) for 0.5 h. The red crystals of **6b** formed were filtered, washed with isopropanol (50 ml) and ether (20 ml) and dried in vacuo (7.4 g, 76%).

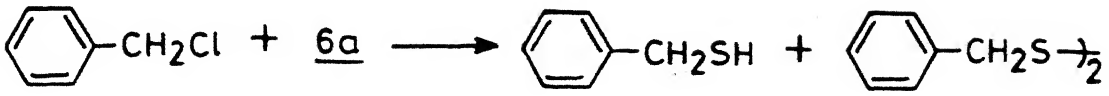
IR (KBr) : 3020, 2990, 2950, 1620, 1600, 1540, 1470, 1440, 1410, 1390, 1300, 1030~1020, 910, 470 cm^{-1}.

$\lambda_{max}^{(CH_3OH)}$: 471 (16980).

Analysis : Calcd for $C_{10}H_{24}N_2S_4Mo$: C, 30.30; H, 6.06; N, 7.07.

Found: C, 30.24; H, 6.12; N, 7.01%.

Reaction of Benzyl chloride **7a** with **6a**



7a 8a 8

To a solution of piperidinium tetrathiotungstate **6a** (1.936 g, 4 mmol) in dimethyl formamide (12 ml) was added dropwise benzyl chloride **7a** (0.508 g, 4 mmol) in dimethyl formamide (4 ml). The reaction mixture was allowed to stir for 1 h. It was worked up as described earlier. Chromatographic purification using petroleum ether (60-80 °C) as eluent gave benzyl thiol **8a** (0.100 g, 20%), b.p. 193 °C and benzyl disulfide **8** (0.332 g, 67%), m.p. 68-70 °C.

Compound 8a

IR (thin film) : 2560 cm^{-1}.

^1H NMR (CCl_4) : δ 1.4-1.56 (t, 1 H); 3.63, 3.73 (d, 2 H); 7.23 (s, 5 H).

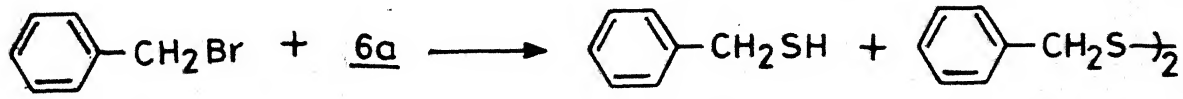
Compound 8

IR (KBr) : 3085, 3030, 2930, 1600, 1495, 1455, 650 cm^{-1}.

^1H NMR (CCl_4) : δ 3.5 (s, 4 H); 7.2 (s, 10 H).

MS (m/e) : 246 (M^+), 214, 182, 121, 91.

Reaction of Benzyl bromide **7b** with **6a**

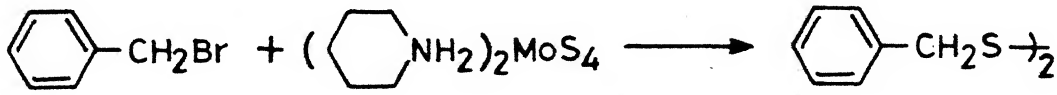


7b 8a 8

To a solution of piperidinium tetrathiotungstate **6a** (1.936 g, 4 mmol) in DMF (12 ml) was added dropwise benzyl bromide **7b**

(0.48 ml, 4 mmol) in DMF (4 ml). The color of the reaction mixture changed instantaneously to dark brown. The reaction was allowed to go for 0.5 h. The reaction was worked up by diluting it with water (100 ml) and extracting it with ether (3x20 ml). The ether extracts were washed with water until the aqueous washings were colorless. The organic layer was dried (anhydrous $MgSO_4$) and the solvent was removed under reduced pressure. Chromatographic purification using petroleum ether (60-80 °C) as eluent gave benzyl thiol **8a** (0.084 g, 17%), b.p. 193 °C (lit.[151] b.p. 194-5 °C) and benzyl disulfide **8** (0.344 g, 70%), m.p. 69-70 °C (lit.[152] m.p. 71-2 °C).

Reaction of Benzyl bromide **7b** with **6b**

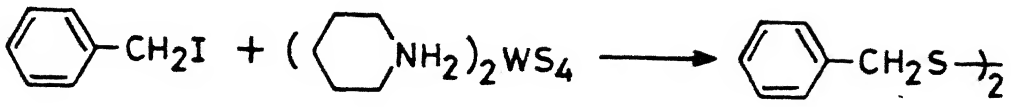


7b **6b** **8**

To a solution of piperidinium tetrathiomolybdate **6b** (1. 980 g, 5 mmol) in DMF (16 ml) was added dropwise benzyl bromide **7b** (0.6 ml, 5 mmol) in DMF (4 ml). Color of the reaction mixture changed instantaneously. The reaction was allowed to go for 0.5 h. It was worked up by diluting it with water (125 ml) and extracting it with ether (3x20 ml). The ether extracts were washed with water until the aqueous washings were colorless. The organic layer was dried (anhydrous $MgSO_4$) and the solvent was removed under reduced pressure. Chromatographic purification using petroleum ether (60-80 °C) as eluent gave benzyl disulfide **8** (0.555 g,

90%), m.p. 69-70 °C as the only product.

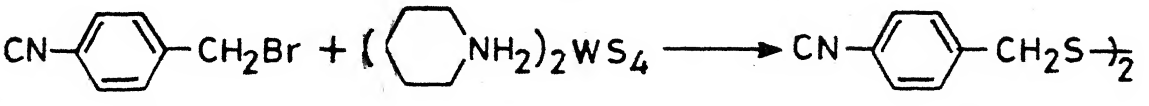
Reaction of compound 7c with 6a



7c 6a 8

To a solution of piperidinium tetrathiotungstate 6a (0.968 g, 2 mmol) in dimethyl formamide (6 ml) was added with stirring benzyl iodide[153] 7c (0.436 g, 2 mmol) in dimethyl formamide (2 ml). The reaction was worked up as described earlier after 0.25 h. Chromatographic purification using petroleum ether (60-80 °C) as eluent gave benzyl disulfide 8 (0.240 g, 98%), m.p. 69-70 °C as the only product.

Reaction of compound 9 with 6a



9 6a 10

To a solution of piperidinium tetrathiotungstate 6a (1.936 g, 4 mmol) in dimethyl formamide (12 ml) was added with stirring p-cyanobenzyl bromide 9[156] (0.784 g, 4 mmol) in dimethyl formamide (4 ml). The reaction mixture was allowed to stir for 0.1 h. It was worked up as described earlier. Concentration of the organic layer yielded pure p-cyanobenzyldisulfide 10 (0.592 g, 100%), m.p. 146-7 °C (lit.[157] 147.5°C).

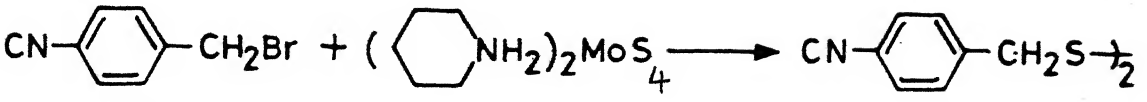
IR (KBr) : 3100, 3000, 2240, 1600, 1220, 760, 540 cm^{-1}.

^1H NMR (CCl_4) : δ 3.66 (s, 4 H); 7.3-7.4 (d, 4 H); 7.63-7.7

(d, 4 H).

MS (m/e) : 296 (M^+), 264, 232, 116.

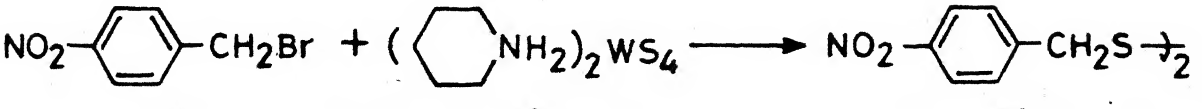
Reaction of compound 9 with 6b



9 6b 10

To a solution of piperidinium tetrathiomolybdate 6b (1.584 g, 4 mmol) in dimethyl formamide (12 ml) was added p-cyanobenzyl bromide 9 (0.784 g, 4 mmol) in dimethyl formamide (4 ml). The reaction mixture was allowed to stir for 0.1 h and was worked up as described earlier. Organic layer was dried (anhydrous $MgSO_4$) and the solvent was removed under reduced pressure. Chromatographic purification using 20% dichloromethane/petroleum ether (60-80 °C) as eluent gave p-cyanobenzyl disulfide 10 (0.384 g, 65%), m.p. 146-7 °C.

Reaction of p-Nitrobenzyl bromide 11 with 6a



11 6a 12

To a solution of piperidinium tetrathiotungstate 6a (1.936 g, 4 mmol) in dimethyl formamide (12 ml) was added with stirring p-nitrobenzyl bromide[154] 11 (0.864 g, 4 mmol) in dimethyl formamide (4 ml). The reaction mixture was worked up

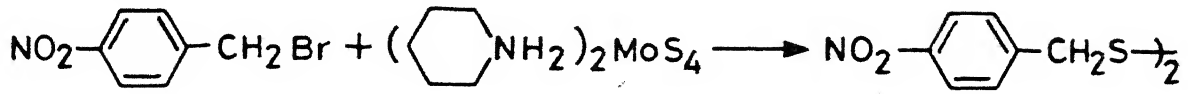
as described earlier after a period of 0.1 h. Chromatographic purification using 15% CH_2Cl_2/petroleum ether (60-80 °C) mixture as eluent gave p-nitrobenzyl disulfide **12** (0.556 g, 83%), m.p. 123-4 °C (lit.[155] m.p. 125 °C).

IR (KBr) : 3100-3020. 1530. 1280, 870, 800 cm^{-1}.

^1H NMR (CCl_4) : δ 3.63 (s, 4 H); 7.36-7.46 (d, 4 H); 8.2-8.3 (d, 4 H).

MS (m/e) : 336 (M^+), 272, 136.

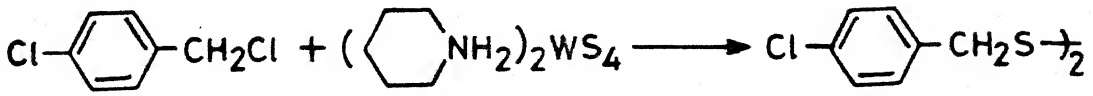
Reaction of **11** with **6b**



11 **6b** **12**

To a solution of piperidinium tetrathiomolybdate **6b** (1.688 g, 3 mmol) in dimethyl formamide (10 ml) was added dropwise p-nitrobenzyl bromide **11** (0.648 g, 3 mmol). The reaction mixture was allowed to stir for 0.1 h. It was worked up as described earlier Chromatographic purification using 15% CH_2Cl_2/petroleum ether (60-80 °C) mixture as eluent gave p-nitrobenzyl disulfide **12** (0.297 g, 59%), m.p. 123-4 °C.

Reaction of p Chlorobenzyl chloride **13** with **6a**



13 **6a** **14**

To a solution of piperidinium tetrathiotungstate **6a** (1.936 g, 4 mmol) in dimethyl formamide (12 ml) was added dropwise with stirring p-chlorobenzyl chloride **13** (0.644 g, 4 mmol) in

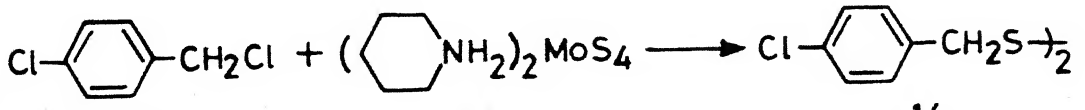
DMF (4 ml). The reaction took 0.5 h to go to completion. It was worked up as described earlier and the crude product, on chromatographic purification using 10% dichloromethane/ petroleum ether (60-80 °C) as eluent gave p-chlorobenzyl disulfide **9f** (0.460 g, 73%), m.p. 57-58 °C (lit.[158] m.p. 58-59 °C).

IR (KBr) : 3000, 1600, 1480, 1400, 1260, 1090, 1010, 810, 720 cm^{-1}.

^1H NMR ($CDCl_3$): δ 3.5 (s, 4 H); 6.9-7.4 (br, 8 H).

MS (m/e) : 315 (M^+), 157, 125.

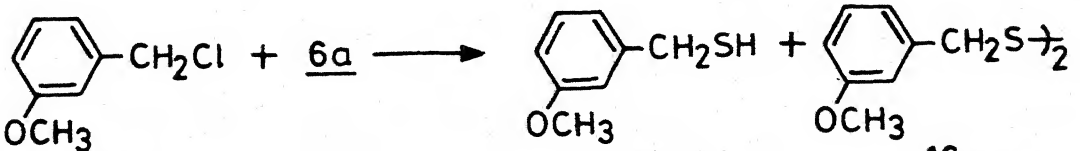
Reaction of p-Chlorobenzyl chloride **13** with **6b**



13 **6b** **14**

To a solution of piperidinium tetrathiomolybdate **6b** (1.584 g, 4 mmol) in DMF (12 ml) was added dropwise with stirring p-chlorobenzyl chloride **13** (0.644 g, 4 mmol) in DMF (4 ml). The reaction was worked up as described above after 0.5 h to give p-chlorobenzyl disulfide **14** (624 mg, 99%), m.p. 57 °C.

Reaction of m-Methoxybenzyl chloride **15a** with **6a**



15a **16a** **16**

To a solution of piperidinium tetrathiotungstate **6a** (1.452 g, 3 mmol) in dimethyl formamide (10 ml) was added dropwise with constant stirring m-methoxybenzyl chlroide **15a**[160] (0.471 g, 3 mmol) in dimethyl formamide (2 ml). The reaction was worked up after 0.75 h the same way as described previously. Chromatographic purification using 20% dichloromethane/petroleum ether (60-80 °C) as eluent gave **16a** (0.105 g, 23%) and **16** (0.348 g, 76%).

Compound 16a

IR (thin film) : 2560 cm^{-1}.

^1H NMR (CCl_4) : δ 1.2 (br, 1 H); 3.73 (s, 3 H); 4.4 (s, 2 H); 6.66-7.0 (br, 3 H); 7.03-7.33 (br, 1 H).

MS (m/e) : 154 (M^+), 121, 107, 95.

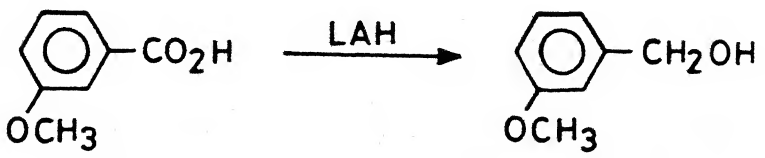
Compound 16

IR ($CHCl_3$) : 3060, 3000, 2950, 2835, 1590, 1480, 1245, 1030, 780 cm^{-1}.

^1H NMR (CCl_4) : δ 3.54 (s, 4 H); 3.76 (s, 6 H); 6.66-6.9 (br, 6 H); 7.06-7.36 (br, 2 H).

MS (m/e) : 306 (M^+), 242, 153, 121.

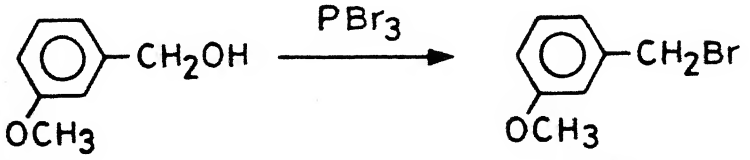
Preparation of m-Methoxybenzyl alcohol



To a slurry of lithium aluminium hydride (2.489 g, 65.5

mmol) in dry ether (40 ml) at 0 °C was added dropwise with stirring m-anisic acid (7.6 g, 50 mmol) in dry ether (50 ml). After the addition was complete , the reaction was refluxed for 24 h, cooled to 0°C and worked up by careful addition of water (2.5 ml), 15% aqueous sodium hydroxide (2.5 ml) and water (2.5x3 ml) and stirred for additional 15 min. It was filtered through a sintered funnel, washed with ether, the filtrate dried (anhydrous $MgSO_4$) and concentrated to give m-methoxybenzyl alcohol (5.959 g, 86.4%), b.p. 128-129 °C/9 mm (lit.[159] b.p. 129-131 °C/9 mm.

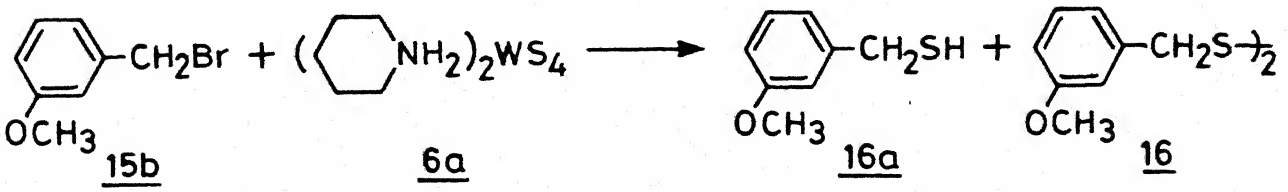
Preparation of m-Methoxybenzyl bromide **15b**



15b

m-Methoxybenzyl alcohol (8.93 g, 0.0647 mol) was treated with 9.5 g (0.035 mol) of PBr_3 in ether (150 ml) overnight. The mixture was hydrolyzed by ice water and the layers separated. The ether layer was washed with $NaHCO_3$ solution, dried (anhydrous $MgSO_4$) and distilled to give m-methoxybenzyl bromide **15b** (116.8 g, 90%), b.p. 122-123 °C/13 mm) lit.[159] b.p. 123-124 °C/13 mm.

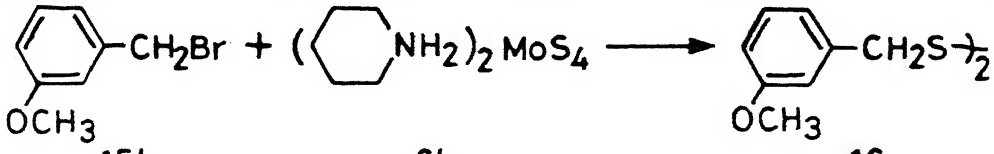
Reaction of m-Methoxybenzyl bromide **15b** with **6a**



15b 6a 16a 16

To a solution of piperidinium tetrathiotungstate **6a** (1.936 g, 4 mmol) in dimethyl formamide (12 ml) was added dropwise with stirring m-methoxybenzyl bromide **15b** (0.804 g, 4 mmol) in dimethyl formamide (4 ml). The reaction took 0.5 h to go to completion. It was worked up the same way as described earlier. Chromatographic purificatiohn using 20% dichloromethane/petroleum ether (60-80°C) as eluent gave the thiol **16a** (0.104 g, 17%) and the disulfide **16** (0.504 g, 82%).

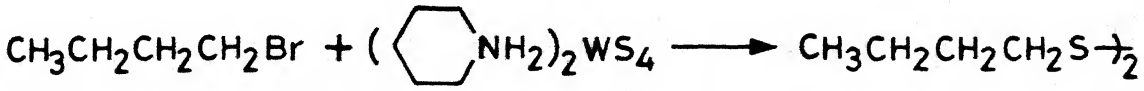
Reaction of m-Methoxybenzyl bromide **15b** with **6b**



15b **6b** **16**

To a solution of piperidinium tetrathiomolybdate **6b** (1.980 g, 5 mmol) in dimethyl formamide (16 ml) was added dropwise with constant stirring m-methoxybenzyl bromide **15b** (1.005 g, 5 mmol) in dimethyl formamide. The reaction took 0.5 h to go to completion. It was worked up in a manner similar to that described earlier. Chromatographic purificationusing 20% dichloromethane/petroleum ether (60-80 °C) as eluent gave **16** (0.560 g, 73%) as the only product.

Reaction of Butyl bromide **17** with **6a**



17 **6a** **18**

To a solution of piperidinium tetrathiotungstate **6a** (1.936 g, 4 mmol) in dimethyl formamide (12 ml) was added with

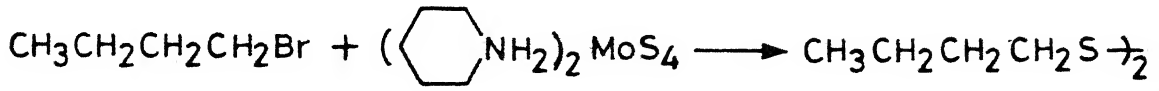
constant stirring butyl bromide **17** (0.548 g, 4 mmol) in dimethyl formamide (4 ml). It took 3 h for the reaction to go to completion. It was worked up as described earlier. Chromatographic purification using 10% ether/petroleum ether (60-80 °C) as eluent afforded the butyl disulfide **18** (0.352 g, 99%), b.p. 96-99 °C/6 mm (lit.[161] b.p. 226 °C).

IR (thin film) : 2960,2860, 1465, 1450, 1375, 760 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 0.88 (s, 6 H); 1.28-1.68 (m, 8 H); 2.70-2.96 (t, 4 H).

MS (m/e) : 178 (M^+), 146, 89.

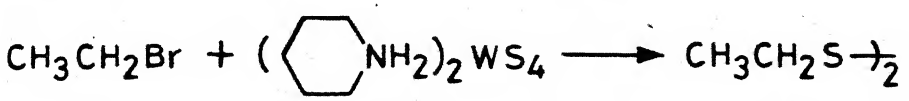
Reaction of Butyl bromide **17** with **6b**



17 **6b** **18**

To a solution of piperidinium tetrathiomolybdate **6b** (1.584 g, 4 mmol) in dimethyl formamide (12 ml) was added with constant stirring butyl bromide **17** (0.548 g, 4 mmol) in dimethyl formamide (4 ml). TLC showed no starting material at the end of 4 h. It was worked up in a manner as described previously. Chromatographic purification using 10% ether/ petroleum ether (60-80 °C) as eluent afforded the butyl disulfide **18** (0.344 g, 97%), b.p. 96-99 °C/6 mm.

Reaction of Ethyl bromide **19** with **6a**



19 **6a** **20**

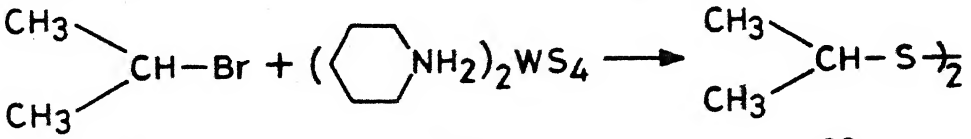
To a solution of piperidinium tetrathiotungstate **6a** (1.452 g, 3 mmol) in dimethyl formamide (10 ml) was added with stirring ethyl bromide **19** (0.327 g, 3 mmol) in dimethyl formamide (2 ml). The reaction mixture was stirred for 0.5 h. It was worked up as described previously. Chromatographic purification using petroleum ether (40-60 ^{o}C) afforded the ethyl disulfide **20** (0.073 g, 40%), b.p. 150 ^{o}C (lit.[162] b.p. 153 ^{o}C).

IR (thin film): 2960, 2855, 1375, 1200, 680 cm^{-1}.

^{1}H NMR (CCl_4) : δ 1.26-1.46 (t, 6 H); 2.83-3.03 (q, 4 H).

MS (m/e) : 122 (M^+), 61.

Reaction of Isopropyl bromide **21** with **6a**



21 **6a** **22**

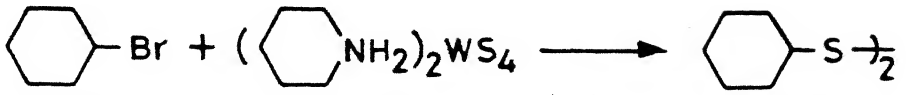
To a solution of piperidinium tetrathiotungstate **6a** (1.936 g, 4 mmol) in dimethyl formamide (12 ml) was added dropwise with constant stirring isopropyl bromide **21** (0.492 g, 4 mmol) in DMF (4 ml). The reaction took 5 h to go to completion. It was worked up the same way as described earlier. Chromatographic purification using 5% ether/petroleum ether (40-60 ^{o}C) gave **22** (0.159 g, 43%), b.p. 95 ^{o}C/56 mm (lit.[162] b.p.177 ^{o}C).

IR (thin film): 1380, 1365 cm^{-1}.

^{1}H NMR(CCl_4) : δ 1.30-1.36 (d, 12 H); 2.95-3.40 (m, 2 H).

MS (m/e) : 150 (M^+), 118, 75.

Reaction of Cyclohexyl bromide **23** with **6a**



23 **6a** **24**

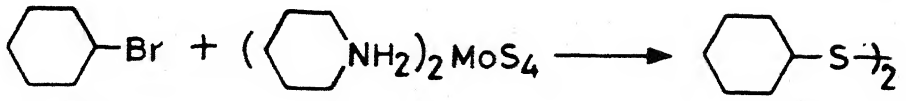
To a solution of piperidinium tetrathiotungstate **6a** (1.936 g, 4 mmol) in dimethyl formamide (12 ml) was added dropwise with constant stirring cyclohexyl bromide **23** (0.652 g, 4 mmol) in DMF (4 ml). The reaction took 12 h to go to completion. It was worked up as described earlier. Chromatographic purification using 5% ether/petroleum ether (60-80°C) as eluent gave **24** (0.392 g, 85%), b.p. 106-110°C/2 mm (lit.[161] b.p. 110-112 °C/2 mm).

IR (thin film): 2926, 2852, 1452, 740 cm^{-1}.

^1H NMR (CCl_4) : δ 1.0-2.16 (br, 20 H); 2.81-3.1 (m, 2 H).

MS (m/e) : 230 (M^+), 115, 83.

Reaction of Cyclohexyl bromide **23** with **6b**

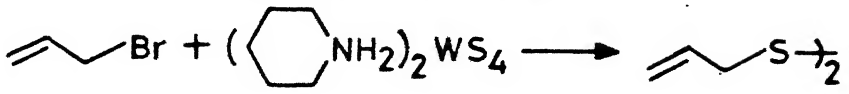


23 **6b** **24**

To a solution of piperidinium tetrathiomolybdate **6b** (1.584 g, 4 mmol) in dimethyl formamide (12 ml) was added with constant stirring cyclohexyl bromide **23** (0.652 g, 4 mmol) in DMF (4 ml). The reaction was worked up after 12 h in the same manner as described earlier. Chromatographic purification using 5% ether/petroleum ether (60-80 °C) as eluent gave **24** (0.350 g,

76%), b.p. 106-110 °C/2 mm.

Reaction of Allyl bromide **25** with complex **6a**



25 **6a** **26**

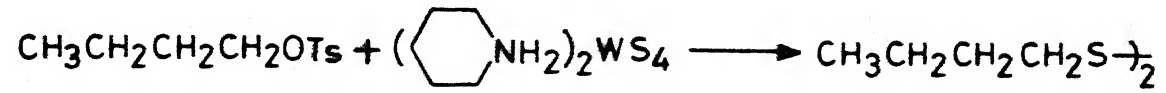
To a solution of piperidinium tetrathiotungstate **6a** (1.452 g, 3 mmol) in dimethyl formamide (4 ml) at 10 °C was added with constant stirring allyl bromide **25** (0.363 g, 3 mmol). The reaction mixture was worked up after 4h ,as described previously,to give allyldisulfide **26**(0.126 g, 58%), b.p.77-78 °C/16 mm (lit.[164] $b.p._{16}$ 78-80 °C/16 mm).

IR (thin film): 1645, 989, 915 cm^{-1}.

^1H NMR (CCl_4) : δ 3.40, 3.45 (d, 4 H); 5.0-5.26 (m, 4 H); 5.61-5.87 (m, 2 H).

MS (m/e) : 146 (M^+), 114, 105, 99, 73, 41.

Reaction of Butyltosylate **27** with **6a**



27 **6a** **18**

To a solution of piperidinium tetrathiotungstate **6a** (1.452 g, 3 mmol) in dimethyl formamide (10 ml) was added dropwise with constant stirring butyltosylate **27** (684 mg, 3 mmol) in DMF (2 ml). The reaction took 13 h to go to completion. It was worked up as described earlier. Chromatographic purification using 10% ether/petroleum ether (60-80°C) as eluent yielded the butyl disulfide **18** (0.186 g, 63.%), b.p. 95-98°C/6 mm (lit.[161] b.p. 226 °C).

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CHAPTER II

CHEMISTRY OF CYCLIC DISULFIDES

2.1 INTRODUCTION

There are a number of methods available in the literature for preparing cyclic disulfides. The preferred method varies with ring size. The common procedures involve either conversion of a dihalide or a ditosylate to a disulfide by displacement with disulfide anion (prepared *in situ* from sodium sulfide and sulfur),[1] or the oxidation of a dithiol by various oxidizing agents; Hydrogen peroxide or ferric chloride often serves well, with high dilution being desirable for rings of more than six members.[2] Iodine with triethylamine has also been recommended.[3] The best method of preparing 1,2-dithiolane system from the corresponding dithiol is by treating it with hydrogen peroxide at 75 ^{o}C[4] (which minimizes polymerization).

1,2-Dithiane can be prepared efficiently by either treating hemitosylate of the dithiol with a base or the corresponding lead thiolate with sulfur.[4] 1,2-Dithiepane can be prepared by treating the corresponding dithiol with ferric chloride.[4]

Cyclic disulfides have also been obtained by the steam

distillation of appropriate Bunte salt.[5] As seen from the Table 2.1, the yields vary greatly with ring size.

There is no relation between the stabilities of the various rings and the yield of the products that are formed. The yield of any ring depends on the probability of the two sulfur atoms being close together at the time the Bunte salt is broken apart. The yield of the trimethylene disulfide is high but it is unstable while the eleven membered ring is relatively stable though the yield is less. These cyclic disulfides tend to go into linear polymers.[6]

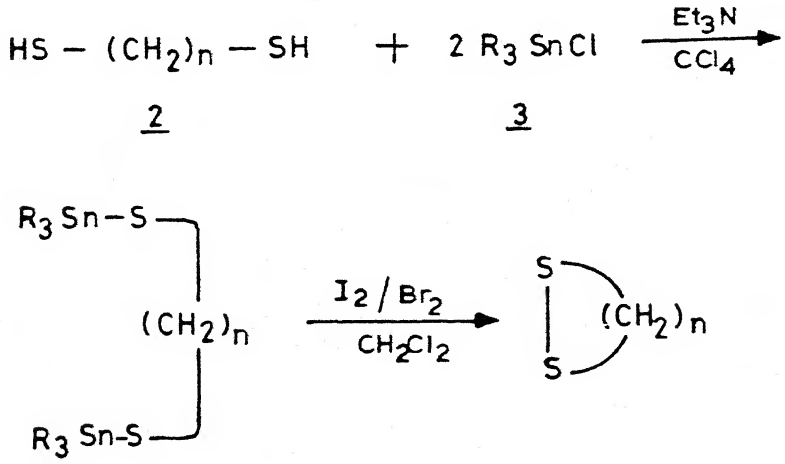
Recently, Harpp et al. have reported the high yield preparation of cyclic disulfides by iodination or bromination of alkyl tin thiolates without the need of high dilution[7] (Scheme 2.1).

1,2-Dithiolanes are interesting cyclic disulfides. They are so nearly planar that the marked distortion from the preferred dihedral angle of 90° evidently figures importantly in the high degree of ring strain they manifest, variously estimated at 16-27 kcal/mole.[8] It is not astonishing therefore that pure 1,2-dithiolanes polymerize so readily that it can be kept well only in solution.[2,4] Substitution for hydrogen atoms at methylene carbon enhances the rate of formation of small and medium sized rings[9] and is attributed in part to the reduction in the number of energetically accessible rotamers in the open chain methyl precursor, relative to the nonsubstituted open chain. This ring is of particular interest, since it is the

Table-2.1

Number members		Yield (%)
4	$-(CH_2)_2-$	Trace
5	$-(CH_2)_3-$	60
6	$-(CH_2)_4-$	22
7	$-(CH_2)_5-$	13
8	$-(CH_2)_6-$	4
9	$-(CH_2)_7-$	2
10	$-(CH_2)_8-$	3
11	$-(CH_2)_9-$	0.2
12	$-(CH_2)_{10}-$	2

Scheme 2.1

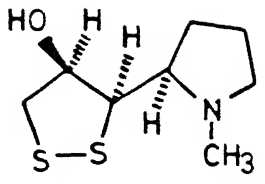


distinctive part of several monocyclic disulfides occurring naturally. Derivatives of the 1,2-dithiolane include the alkaloid brugine **47** and gerrardine **48**[10] the neurotoxic compound nereistoxin **46** from the marine worm,[11] the acid from asparagus **41**,[12] compounds from cabbage believed to be 1,2-dithiole-3-thiones **40**,[13] charatoxin from the green fresh water alga chara globularis **45**,[14] α-lipoic acid **37**[15] and the new sulfur containing insecticidal alkaloids Guinesine A **44a**, B **44b**, C **44c** from cassipourea guianensis[16] (**Scheme 2.2**).

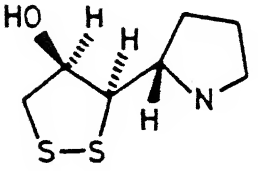
The endodisulfide analogue of PGH_2, methyl (5Z,9α,11α, 13E, 15S)-9,11-epidithio 15-hydroxyprosta-5,13-dienoate **63**, is of special interest, since the dithio linkage is more stable chemically than a peroxide unit and the molecular geometry of the rigid endodisulfide ring system approximates that of PGH_2.[1]

α-Lipoic acid **37** has been of interest to biological chemists for some time but particularly since its isolation[18] and identification.[19] Interest in the total synthesis of α-lipoic acid **37** arose because of its physiological properties.[18,20] Lipoic acid **37** is one of the coenzymes of an enzyme complex that catalyze oxidative decarboxylation of α-keto carboxylic acids.[18,20,21] It is a growth factor[22] for a variety of microorganisms and it reduces the blood sugar of diabetic rabbits during a glucose tolerance test.[23] Calvin and coworkers[24] postulate that lipoic acid participates in the primary photochemical reaction of photosynthesis. In more

Scheme 2.2



44a
Guinesine A



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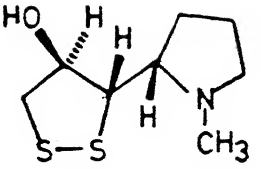
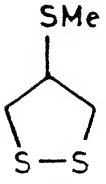
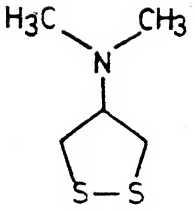
Guinesine B



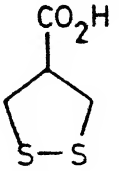
44c
Guinesine C



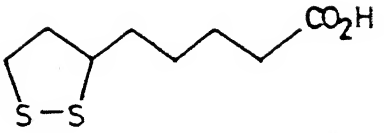
45
Charatoxin



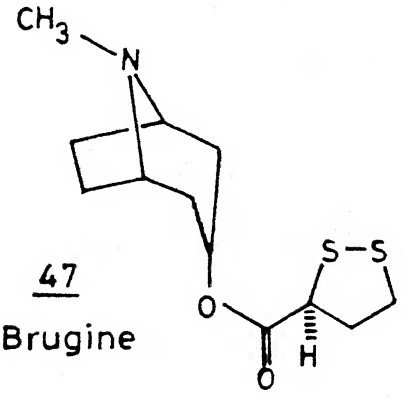
46
Nereistoxin



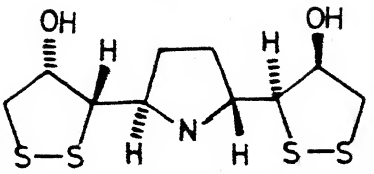
41
Asparagusic acid



47
α - Lipoic Acid



47
Brugine



48
Gerrardine

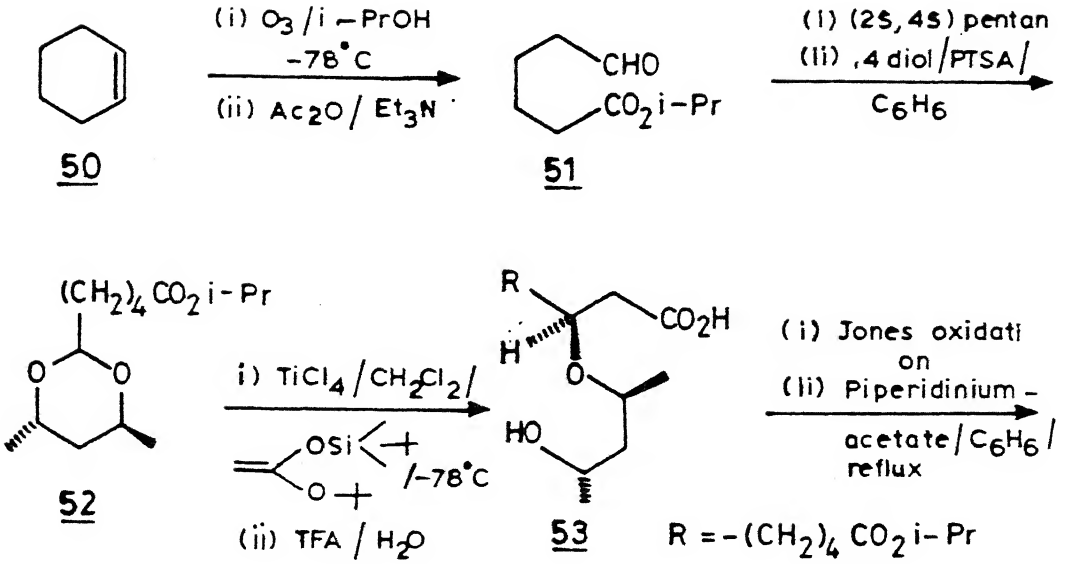
recent modification of the postulation,[25] the role of lipoic acid is depicted in a reaction sequence analogous to its role in α-keto oxidation. It appears to aid in the functioning of certain enzymes[26,27] and the mechanism for its action has been proposed.[27] Although the coenzyme activity is confined to the (+) isomer, the (±) form is equally important in medicine in view of the fact that the presence of the (-) isomer has no detrimental effect on the therapeutic value.[23] Lipoic acid which has been rather thoroughly studied clinically,[28] has an acute toxicity in animals at a value of 100 to 1000 times its therapeutic dose.

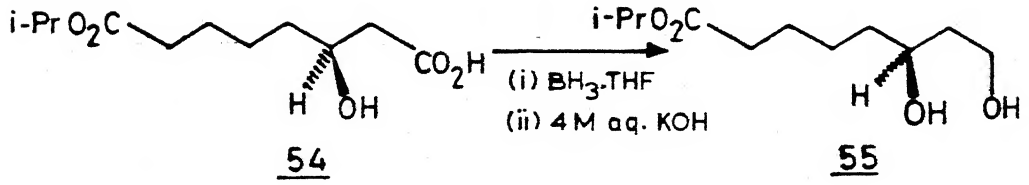
Although several syntheses of (±) lipoic acid **37** have been reported, natural R (+) lipoic acid **37** has been obtained by resolution of the racemate.[29] The first asymmetric synthesis of (+) lipoic acid was reported by Elliott and coworkers[30] in which the rather expensive S,S pentane 2,4-diol was used as the starting material and source of optical activity (**Scheme 2.3**).

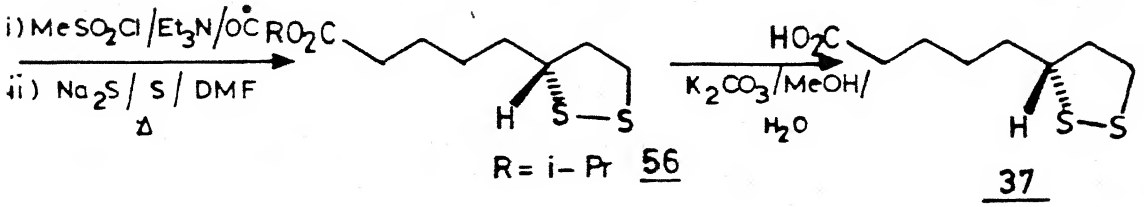
Lately a number of strategies have been put forth for the synthesis of optically active α-lipoic acid.[15b] The R configuration of (+) lipoic acid has been confirmed by Golding[31] by a synthesis of the unnatural (-) antipode from the S-malic acid. A synthesis of the natural enantiomer has been completed by the same group starting from S-malic acid.[15b] (**Scheme 2.4**).

Asparagusic acid has been obtained from the roots and edible portions of <u>asparagus officialis</u>.[32,33] This dithiolane is a plant growth inhibitor exhibiting activity comparable to

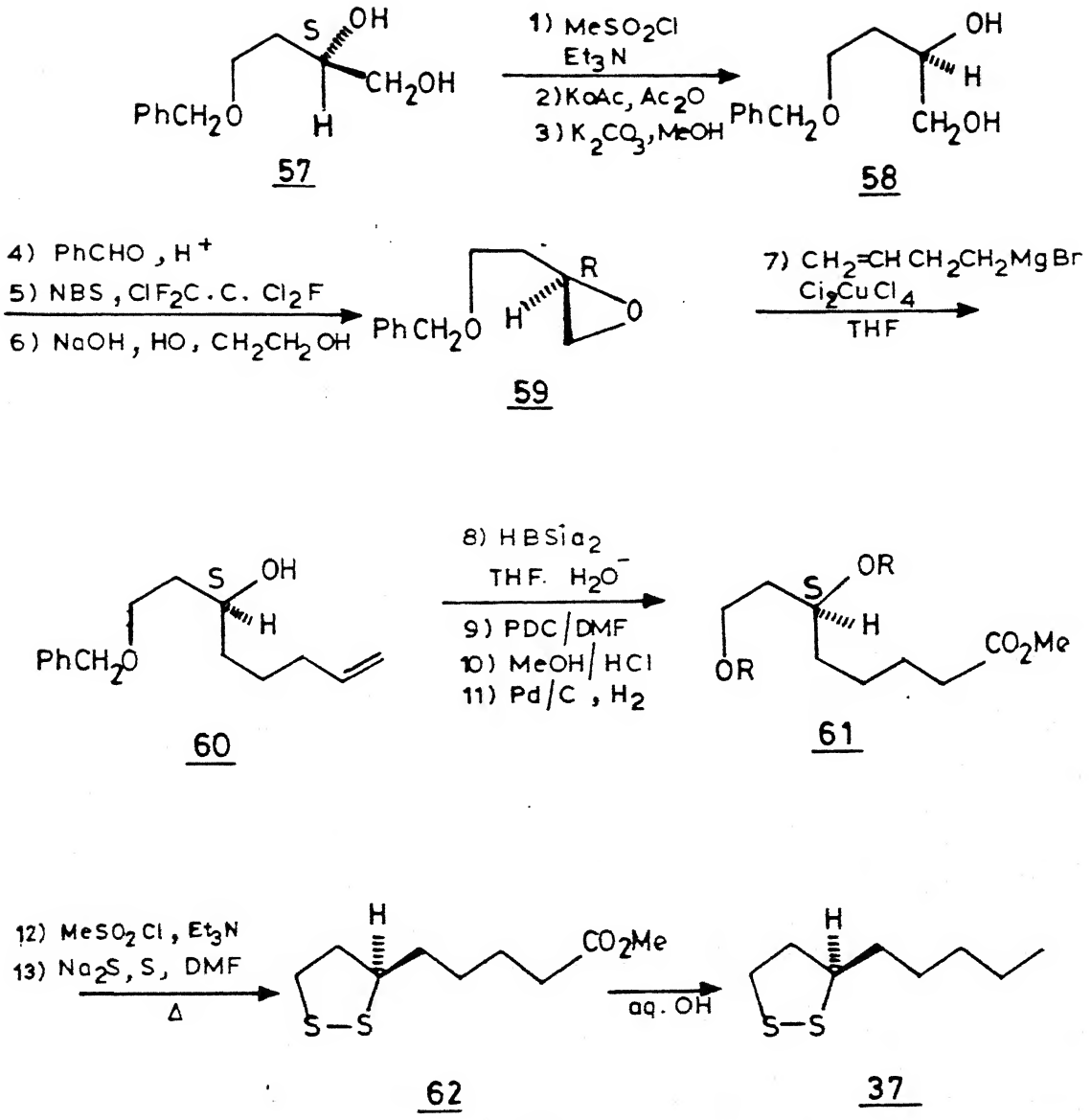
Scheme 2.3


(i) O3 / i-PrOH
-78°C
(ii) Ac2O / Et3N
CHO
CO2i-Pr
(i) (2S,4S) pentan
(ii) ,4 diol/PTSA/
C6H6
50
51
(CH2)4CO2i-Pr
i) TiCl4 / CH2Cl2/
OSi
O
/-78°C
(ii) TFA / H2O
R
CO2H
H
O
HO
(i) Jones oxidati
on
(ii) Piperidinium -
acetate/C6H6/
reflux
52
53
R = -(CH2)4 CO2 i-Pr


i-Pr O2C
CO2H
H
OH
i-PrO2C
(i) BH3.THF
(ii) 4 M aq. KOH
H
OH
OH
54
55

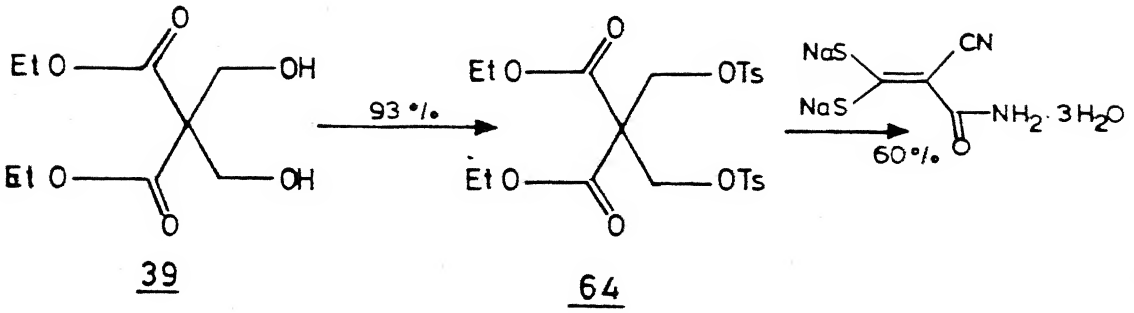

i) MeSO2Cl /Et3N/OC RO2C
ii) Na2S / S / DMF
Δ
H
S—S
HO2C
K2CO3/MeOH/
H2O
R= i- Pr
56
37

Scheme 2.4

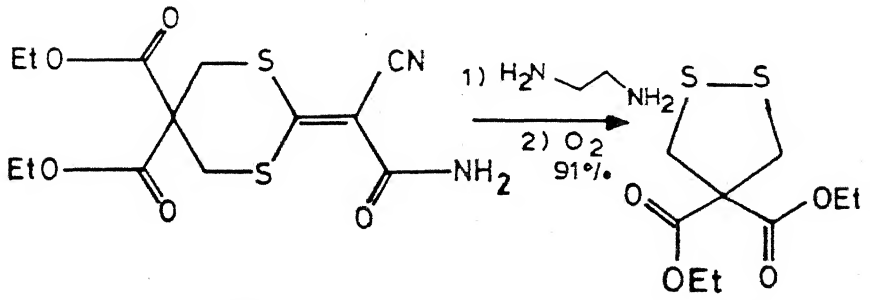


57 58 59 60 61 62 37

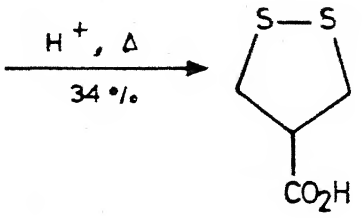
Scheme 2.5



39 64



65 66



41

abscisic acid[32,33] and it also possesses potent nematicidal activity.[33] Synthetic procedures for this compound have been reported,[34] however, all these procedures have inherent problems arising from the instability of the precursors and/or formation of product mixtures which are difficult to separate. Christopherson and Teuber[35a] reported a modified procedure for the synthesis of 4-substituted 1,2-dithiolanes which allows a better controlled preparation. Unfortunately, the yield obtained by this method is very low (33%) (**Scheme 2.5**).

Our interest in the chemistry of cyclic disulfides, in general, and the synthesis of some naturally occurring 1,2-dithiolanes, in particular, arose from the fact that our methodology of novel alkylation with tetrathiometallates (**Chapter I**) could be extended to intramolecular reactions as well. Most of the syntheses reported thus far, for forming the crucial S-S bond in an intramolecular reaction of 1,3-dihalides or dimesylates involve treatment with Na_2S/S reagent system.[1] The reaction conditions are not that mild and yields of the products are only moderate. In this chapter we present our work on the successful synthesis of cyclic disulfides using tetrathiometallates and the application of this methodology to the synthesis of asparagusic acid **41** and (±) α-lipoic acid **37**.

2.2 RESULTS AND DISCUSSION

Synthesis of Cyclic disulfides with Tetrathiotungstates

Having shown the efficacy of tetrathiometallates (MS_4^{2-})

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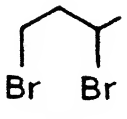
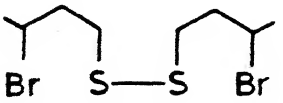
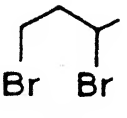
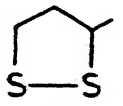
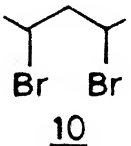
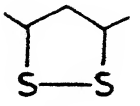
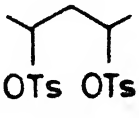
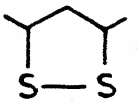
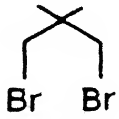
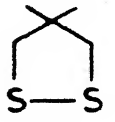
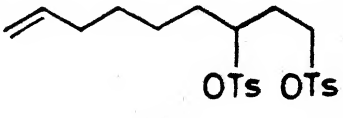
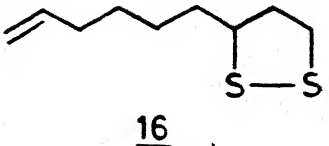
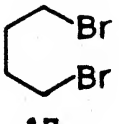
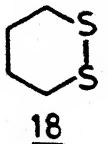
2	 7	28	4	 8	54
3	 7	60	4	 9	61
4	 10	28	5	 11	62
5	 12	28	12	 11	56
6	 13	28	6	 14	68
7	 15	28	12	 16	54
8	 17	28	3	 18	74

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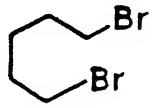
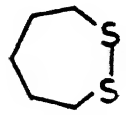
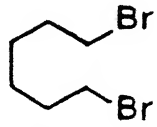
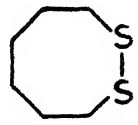
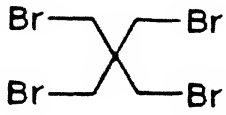
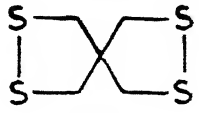
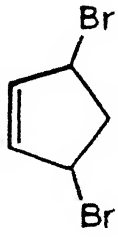
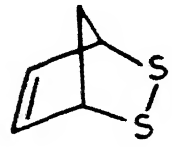
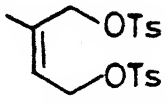
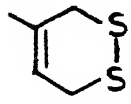
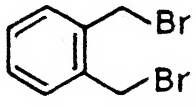
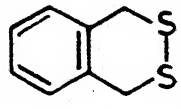
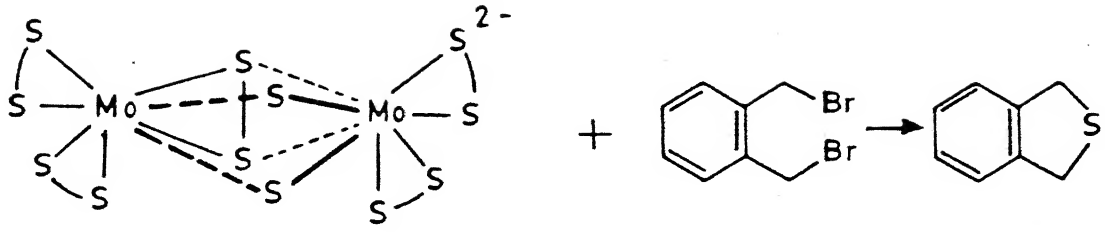
9	 19	28	5	 20	50
10	 21	28	8	 22	46
11	 23	28	12	 24a	13
				 24	55
12	 25	0	12	 26	20
13	 27	28	18	 28	43
14	 29	28	4	 30	94

of molybdenum and tungsten in bringing about the formation of disulfides from alkyl halides in intermolecular reactions (Chapter I), it was of interest to find out whether cyclic disulfides can be formed efficiently from (1,n) dihalo compounds via intramolecular pathway.

Harpp and MacDonald[36a] have earlier shown that the persulfido complex, $Mo_2S_{12}^{2-}$, **1** on treatment with α,α'-dibromo-o-xylene **29**[36b] in a sealed tube at 90 °C for 20 h gave 1,3-dihydroisothianaphthalene **30a** as the only product in 67% yield (**Scheme 2.6**). However, treatment of 2-bromo-2-methylpropane **66**, 2,6-dibromocyclohexanone **67** or 1,3-dibromopropane **4** with the persulfide reagent **1** in benzene or acetonitrile gave only the starting materials even after prolonged heating (**Scheme 2.6**). Interestingly, reaction of piperidinium tetrathiotungstate **6** with α,α'-dibromo-o-xylene **29** (DMF, 28 °C, 4 h) afforded the cyclic disulfide **30**[36c] as the only product in excellent yield (94%)[37] (**Scheme 2.7**).

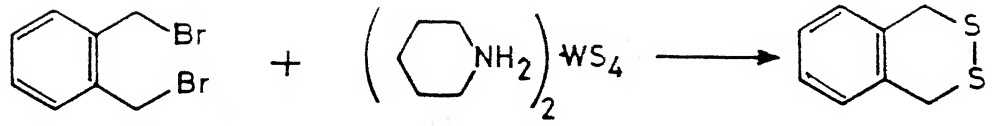
Treatment of 1,3-dibromobutane **7**[38] with **6** at room temperature (~28 °C) initially posed a few problems. We obtained the dimer **8** instead of the desired 3-methyl 1,2-dithiolane system **9**[37a]. This probably results from a higher order of reactivity of primary bromide, compared to the secondary bromide. This problem, however, was overcome by carrying out the reaction in the dark at a higher temperature (60 °C for 4 h) and in more dilute solution. In this case 1,2-dithiolane **9** was obtained in 61% yield (**Scheme 2.8**).

Scheme 2.6



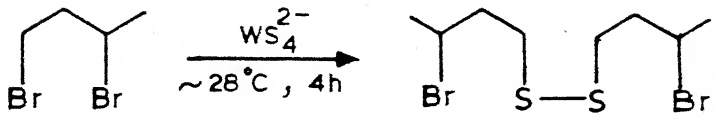
1 29 30a

Scheme 2.7

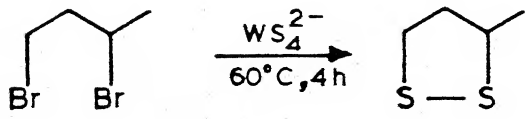


29 6 30

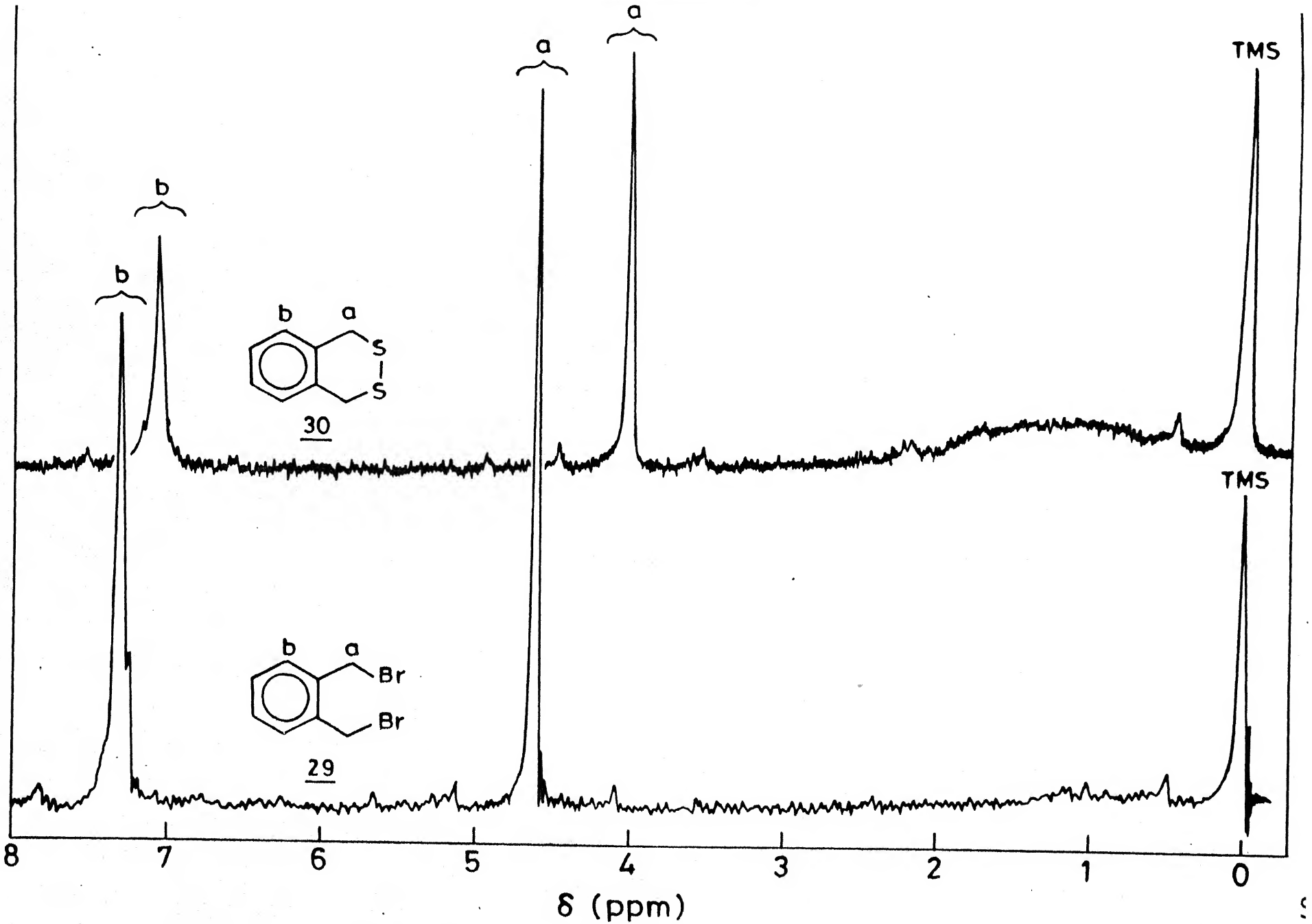
Scheme 2.8



7 8



7 9



^{1}H NMR spectrum (90 MHz) of 29 & 30

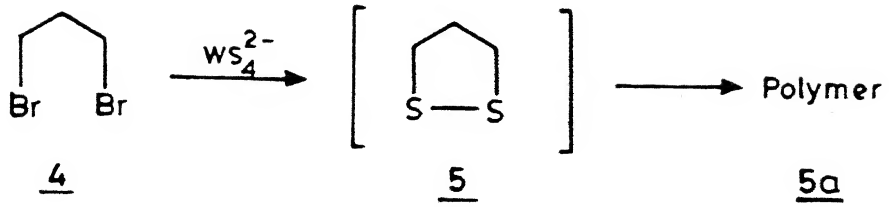
The reaction of 1,3-dibromopropane **4** with **6** took place readily at room temperature (28 ^{o}C, 2 h). However, attempts to isolate pure 1,2-dithiolane system **5** always led to polymerized material **5a**.[39] This is in accordance with the earlier observation[2,4] that unsubstituted dithiolane systems are prone to polymerization (**Scheme 2.9**).

2,2-Dimethyl-1,3-dibromopropane **13**[40] was prepared by the reaction of 2,2-dimethyl-1,3-propane diol with PBr_3. Compound **13** on treatment with **6** (28 ^{o}C, 6 h) gave the corresponding 4,4-dimethyl-1,2-dithiolane **14** in 68% yield. Compound **10**[42] under similar reaction conditions, on treatment with **6** (DMF, 28 ^{o}C, 5 h) afforded the 1,2-dithiolane **11**[39,43] in 62% yield. Compound **11** was also obtained as the only product (56%) by reaction of ditosylate **12**[1b] with **6** (DMF, 28^{o}C, 12 h) (**Scheme 2.10**).

Similarly when the ditosylate **15** was treated with one equivalent of **6** (DMF, 12 h), the corresponding 1,2-dithiolane system **16** was obtained in 54% yield (**Scheme 2.11**).

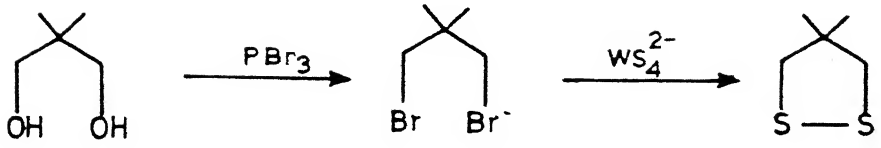
In order to find out whether the present methodology could be effectively extended to synthesize higher cyclic dithia-analogues, we treated 1,4-dibromobutane **17**, 1,5-dibromopentane **19** and 1,6-dibromohexane **21**, with **6** and obtained the corresponding dithiane **18**,[4] dithiepane **20**[4,44] and dithiaoctane **22**[4,44] in 74%, 50% and 46% yield, respectively (**Scheme 2.12**). At this point it was decided to gauge the scope of this novel reaction to the formation of disulfide which is part of a spiro cyclic

Scheme 2.9

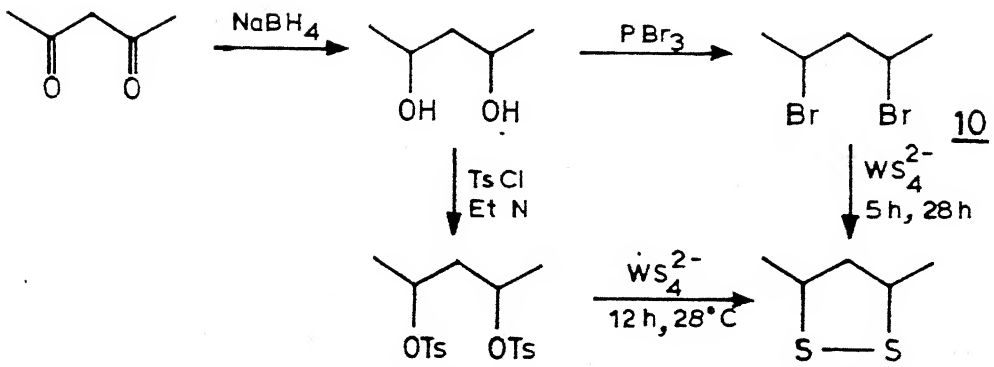


4 5 5a

Scheme 2.10

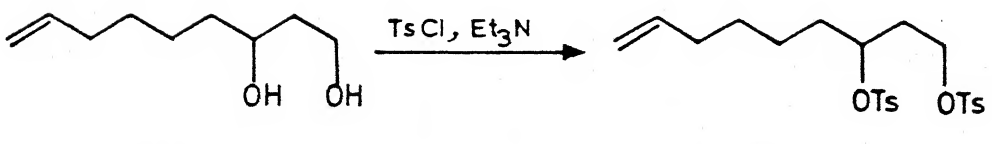


13 14

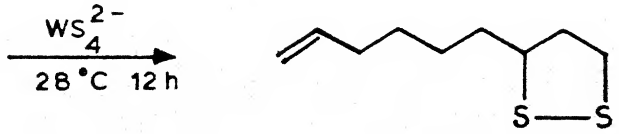


12 11

Scheme 2.11



34 15



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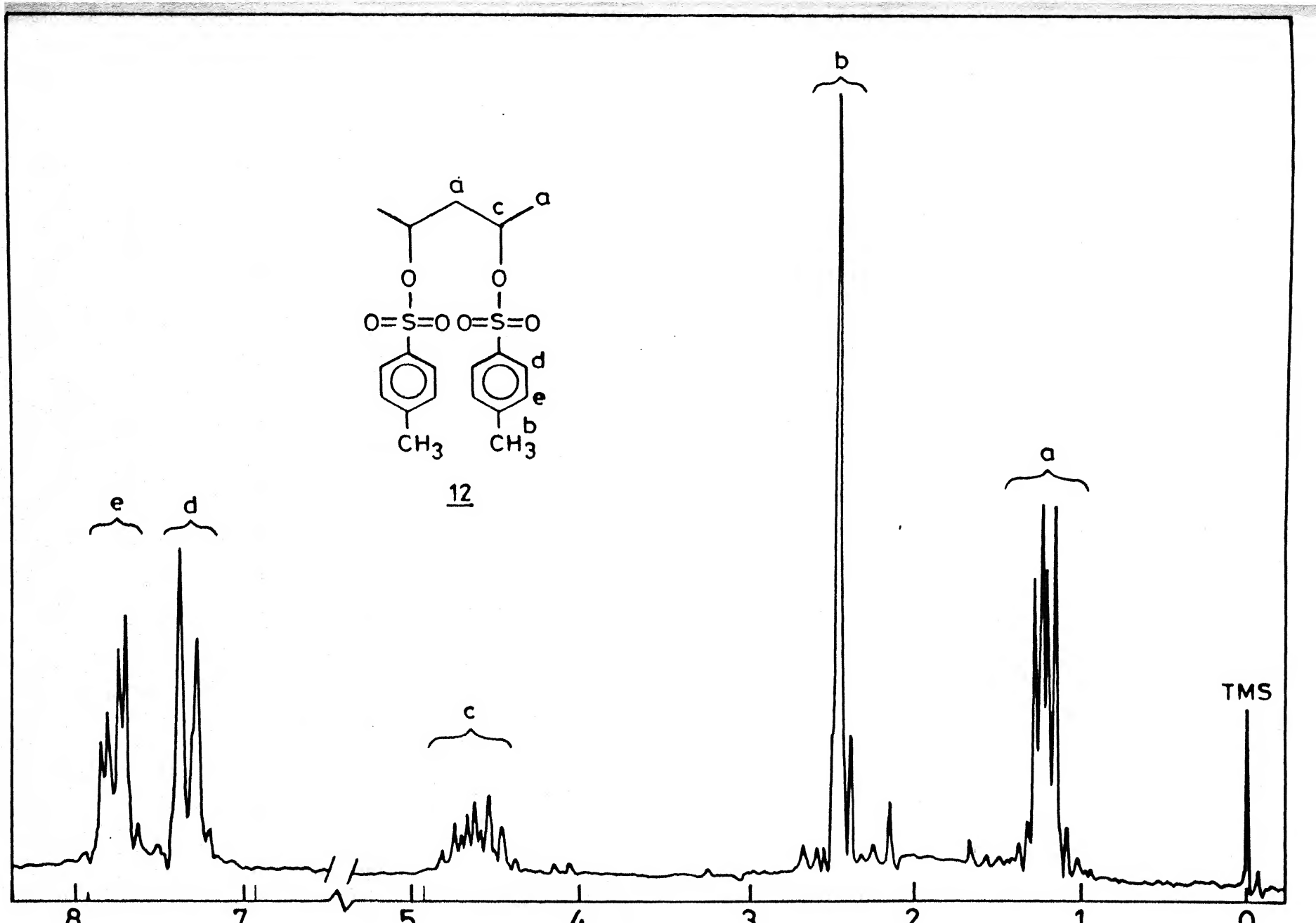
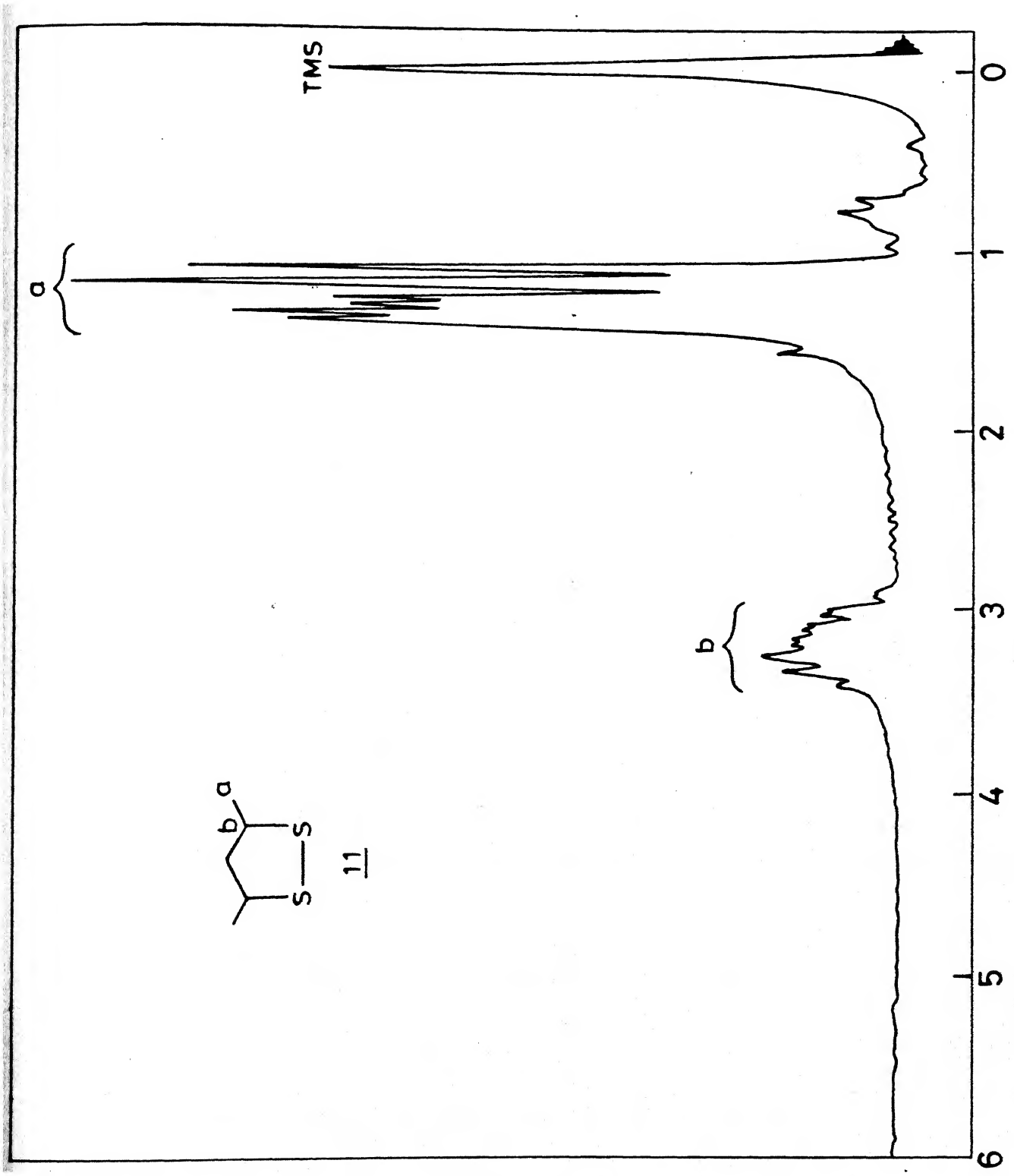
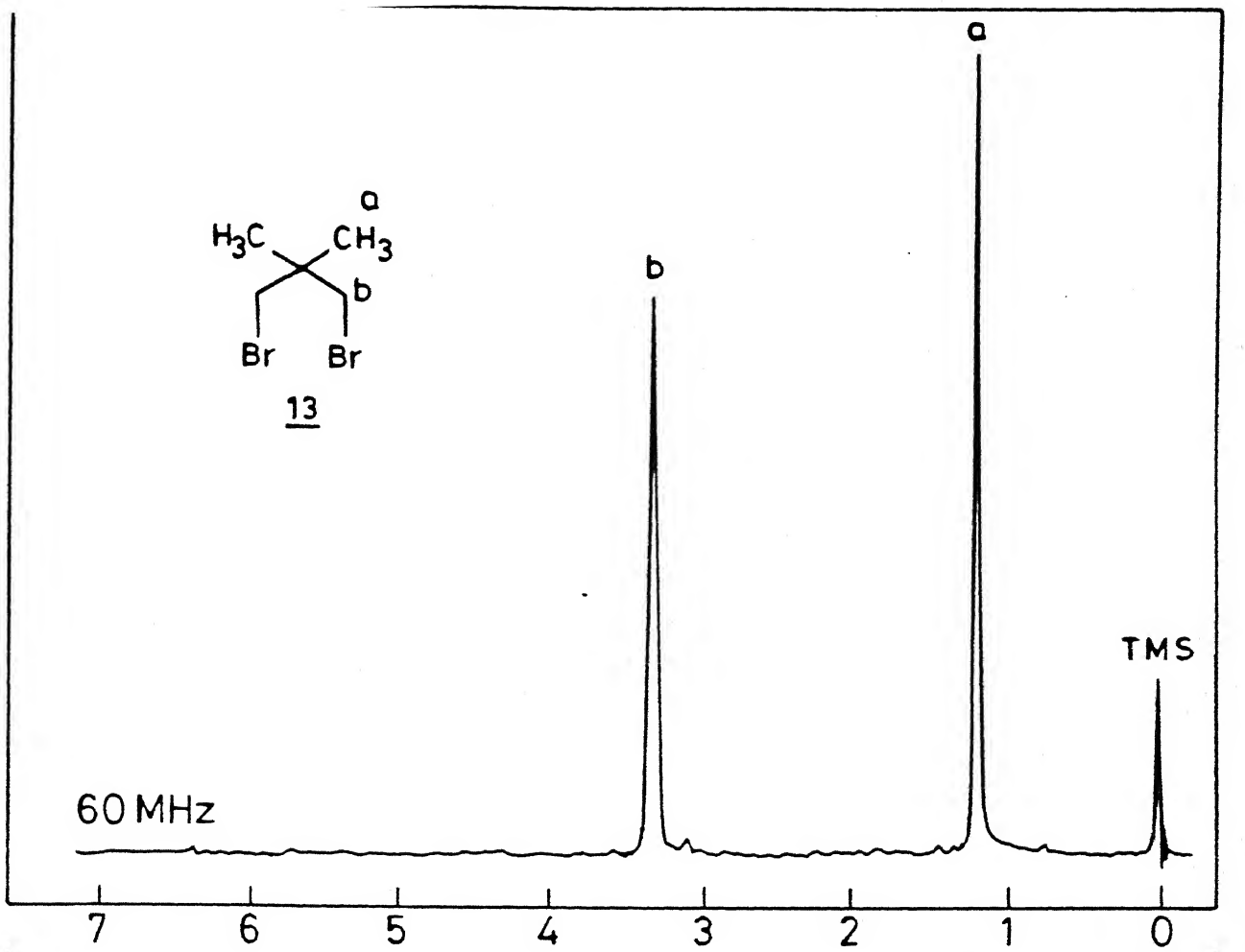


^{1}H NMR spectrum (80 MHz) of 12



^{1}H NMR spectrum (80 MHz) of 11



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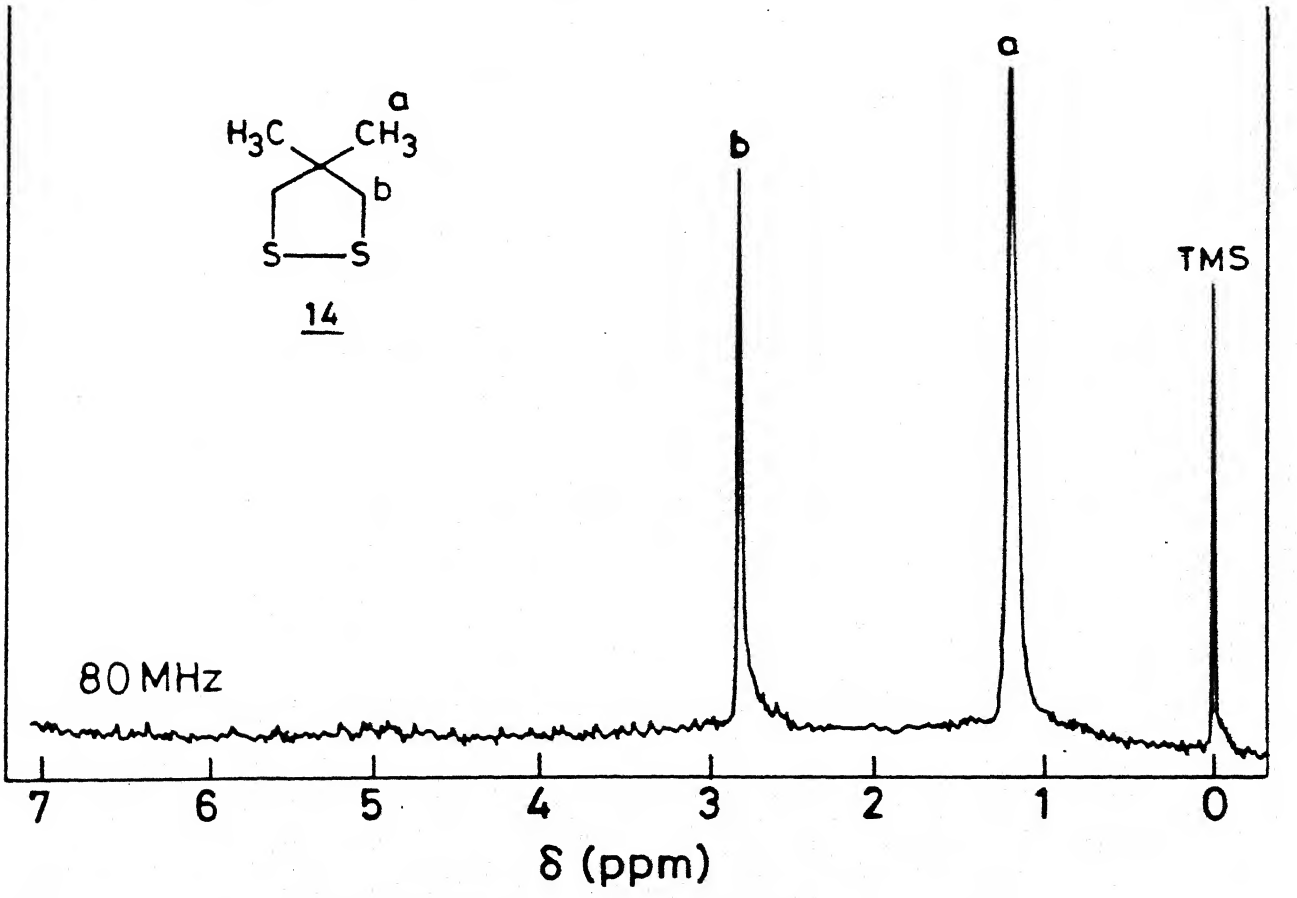
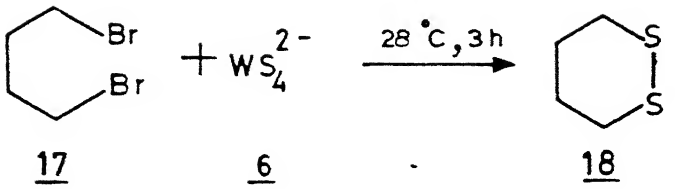


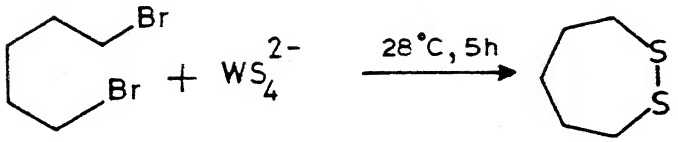
14

^{1}H NMR spectra of 13 & 14

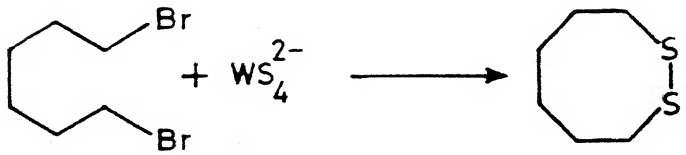
Scheme 2.12



17 6 18

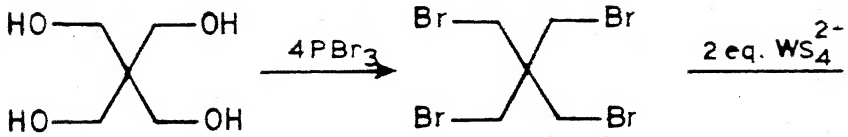


19 6 20



21 6 22

Scheme 2.13



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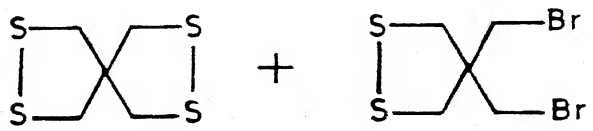
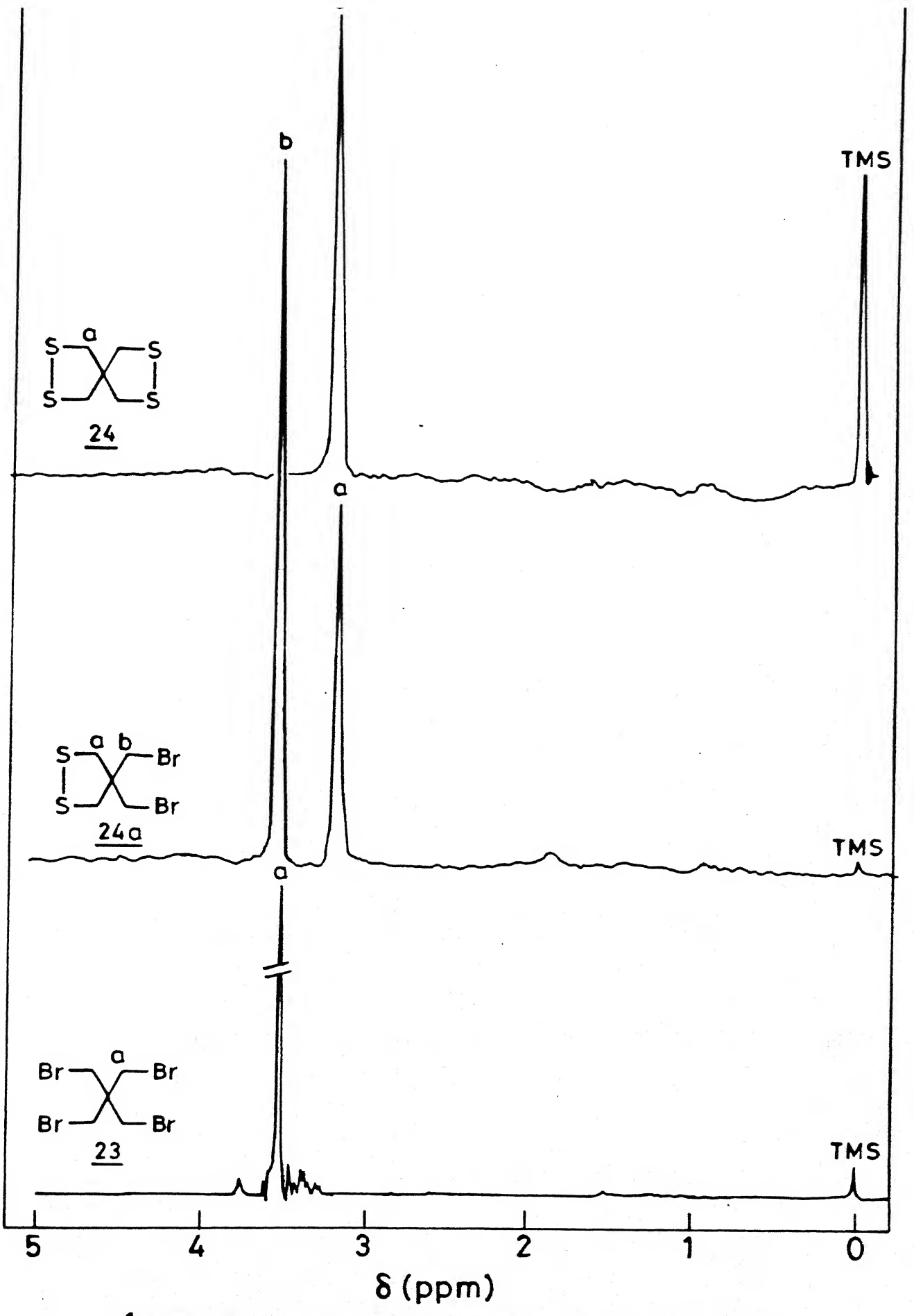
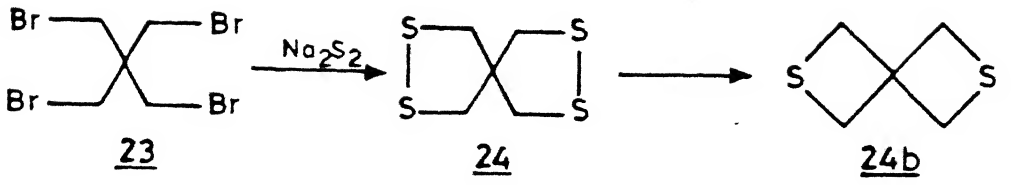


24 24a

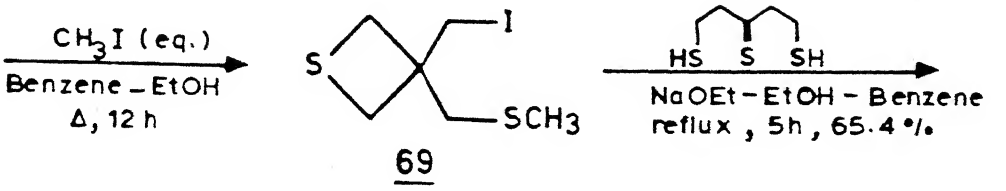


^{1}H NMR spectra (80 MHz) of 23 , 24a & 24

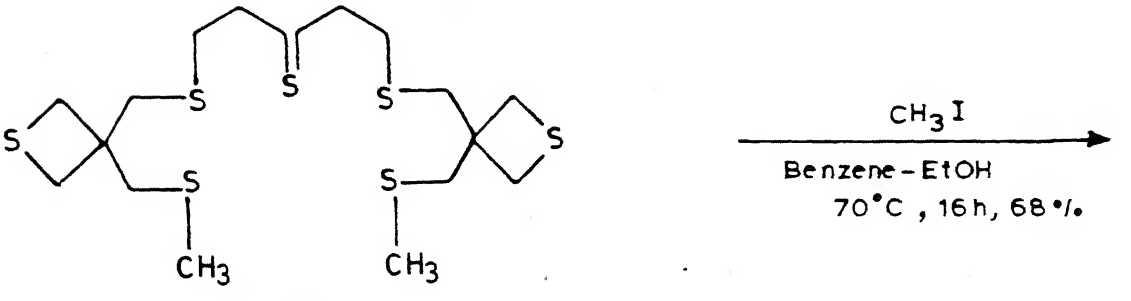
Scheme 2.14



23 24 24b



69



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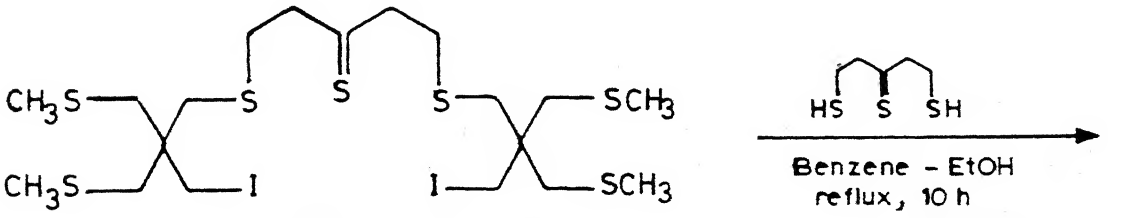
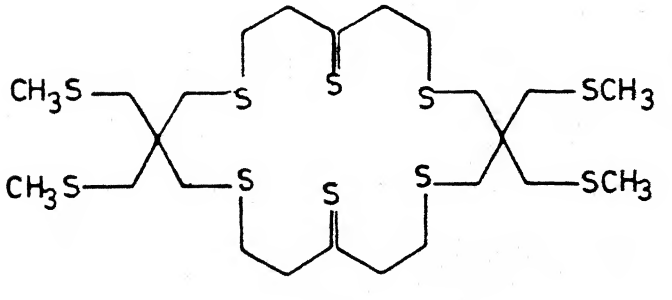


71

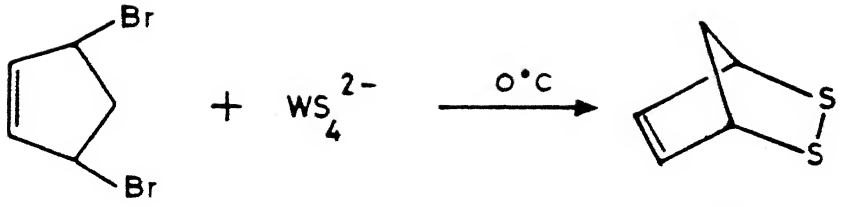


72

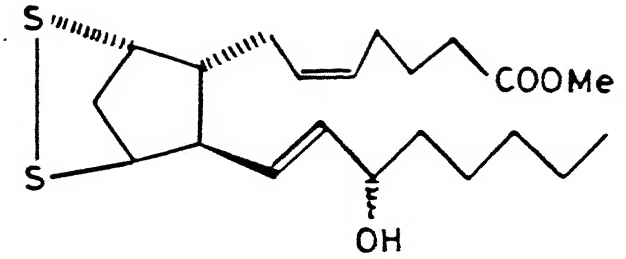
system. Accordingly, the tetrabromo compound **23**[45] derived from pentaerythritol was allowed to react with two mole equivalents of **6** (DMF, 28 °C, 12 h). The tetrathiaspiro compound **24** (55%), the dibromodithiolane **24a** (13%) and unreacted starting material **23** (6%) were isolated from this reaction after chromatographic purification (**Scheme 2.13**). The spiro compound **24** has recently been prepared by Christopherson and Teuber[35a] from **23** in two steps in 18% yield. This tetrathiospiro compound **24** has been used by Fijihara and coworkers for the synthesis of crown thioether **72**.[35b] (**Scheme 2.14**).

Another compound of interest was the bicyclic dithianorbornene **26**. 3,5-Dibromocyclopentene **25**,[37b] when treated with **6** at 0 °C for 12 h gave the bicyclic compound **26** in 20% yield (**Scheme 2.15**). The low yield of **26** in this reaction can be attributed to the unstable nature of the starting material and highly volatile nature of product.

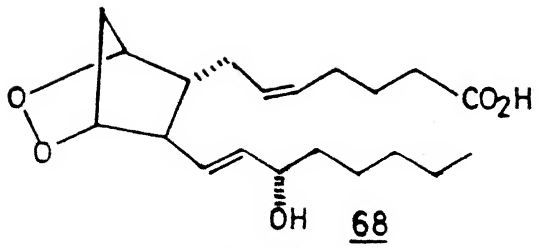
Considerable effort has recently been focussed on the synthesis of stable analogues of the prostaglandin endoperoxide **68** as its short life of only 5 minutes in aqueous buffer has presented a problem in studying its biological action.[17] The endodisulfide analogue of PGH_2 **73** is of special interest since a dithio-linkage is more stable chemically than a peroxide unit and the molecular geometry of the rigid endodisulfide ring system approximates that of PGH_2. A number of syntheses for this dithia analogue of prostaglandin endoperoxide have been reported in the recent past.[17] It appears



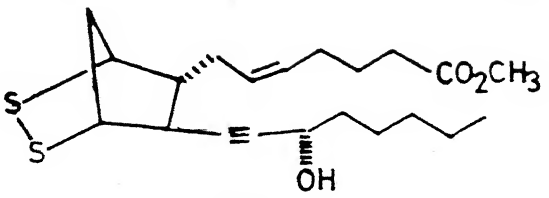
25 26



63

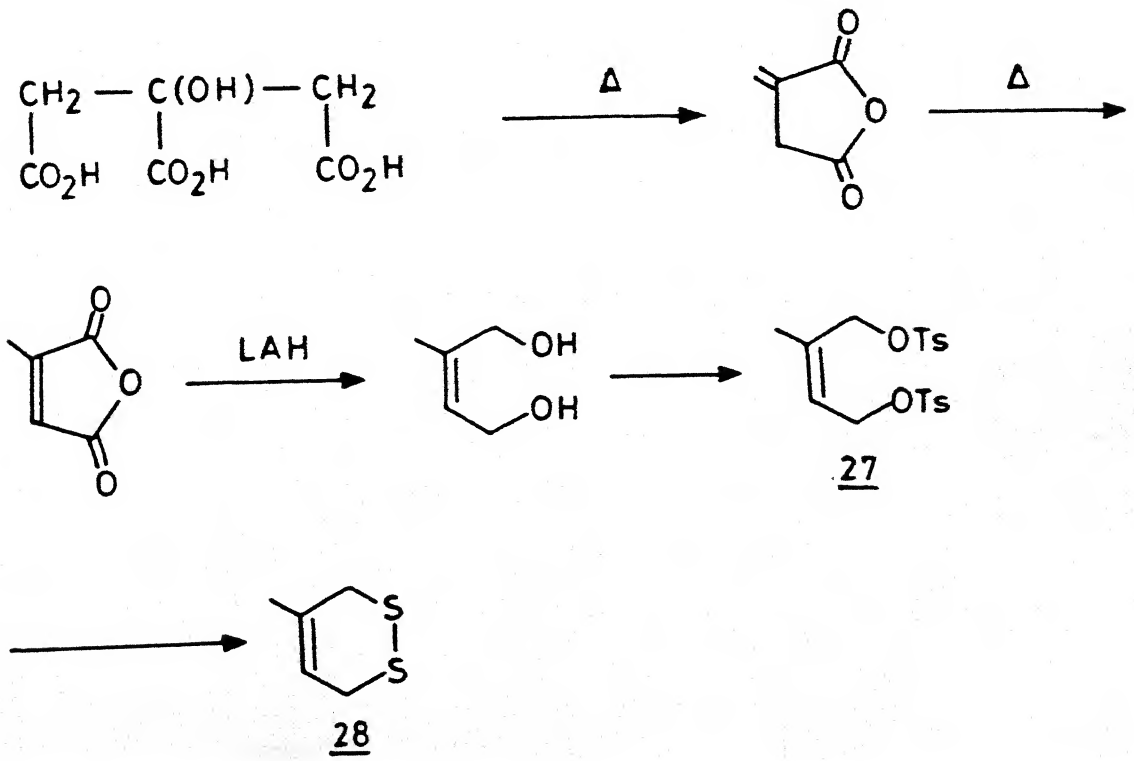


68



73

Scheme 2.16



27 28

that our methodology would provide easy access to some key intermediates in the synthesis of **73** and related compounds.

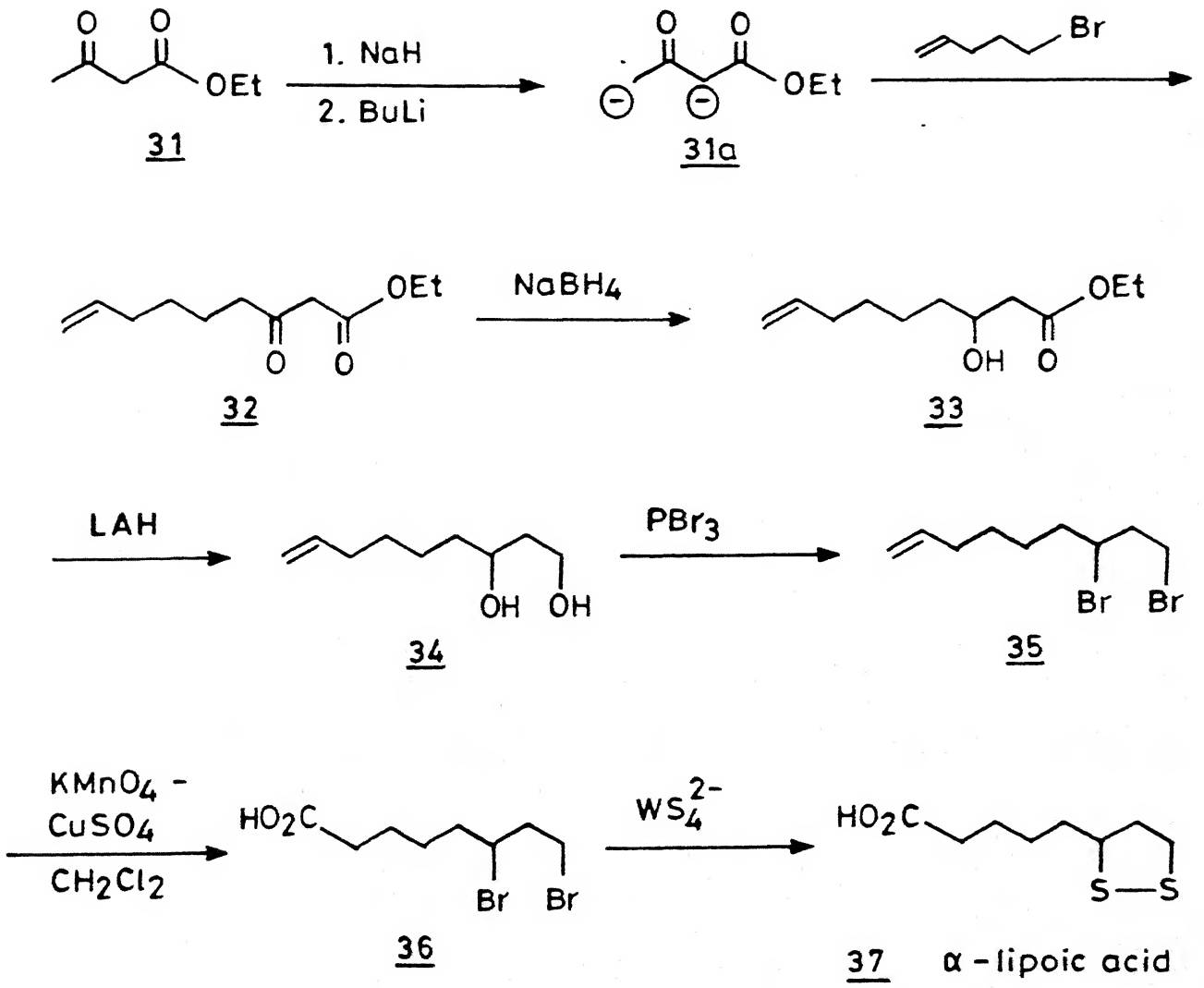
Another allylic cyclic disulfide **28** was prepared by the reaction of ditosylate **27** with **6**. The reaction took 18 h to go to completion and gave the disulfide **28** in 43% yield. The ditosylate was prepared from citric acid in 4 steps (**Scheme 2.16**).

Having demonstrated the usefulness of piperidinium tetrathiotungstate **6** in the formation of cyclic disulfides from the corresponding dihalo compounds or ditosylates, it was decided to apply this methodology to the synthesis of (±) α-lipoic acid **37** and asparagusic acid **41**.

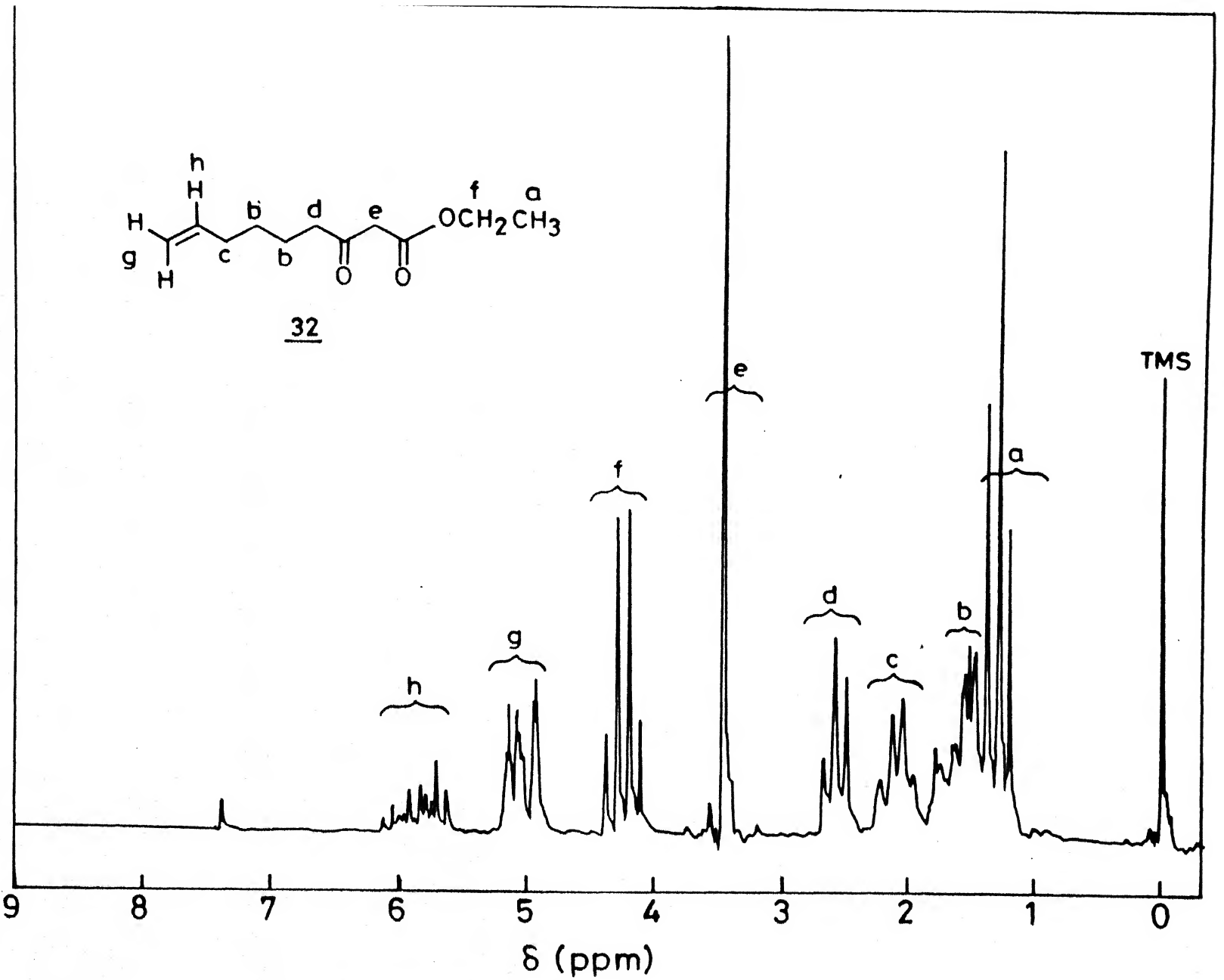
Synthesis of α-Lipoic Acid **37**

In designing an efficient synthesis of dl-α-lipoic acid **37**, two problems have to be considered. The first one is the selection of proper building blocks for the eight carbon chain and the second problem is the method of forming the dithiolane system. For this purpose usually 1,3-diols, tosylates and halides were converted to the dithiols by the reaction of sulfur compounds such as sodium disulfide,[29b] thioacetic acid,[46] benzyl mercpatan[46] and thiourea.[3] We have utilized our novel alkylation using metal-sulfur derivatives as the key step in the formation of the crucial sulfur-sulfur bond. The strategy followed for the synthesis of (±) lipoic acid from acetoacetic ester is outlined in **Scheme 2.17**.

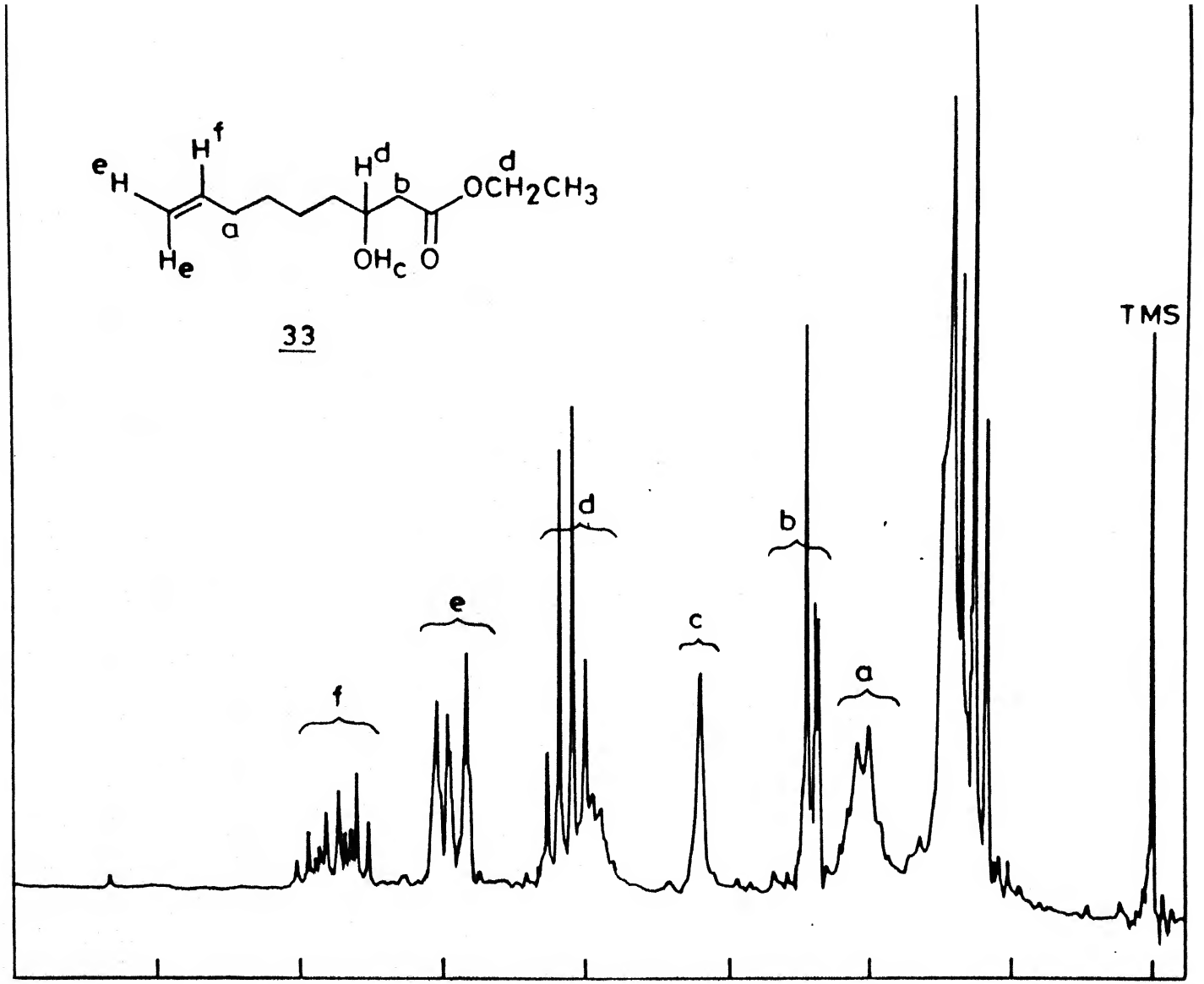
Scheme 2.17



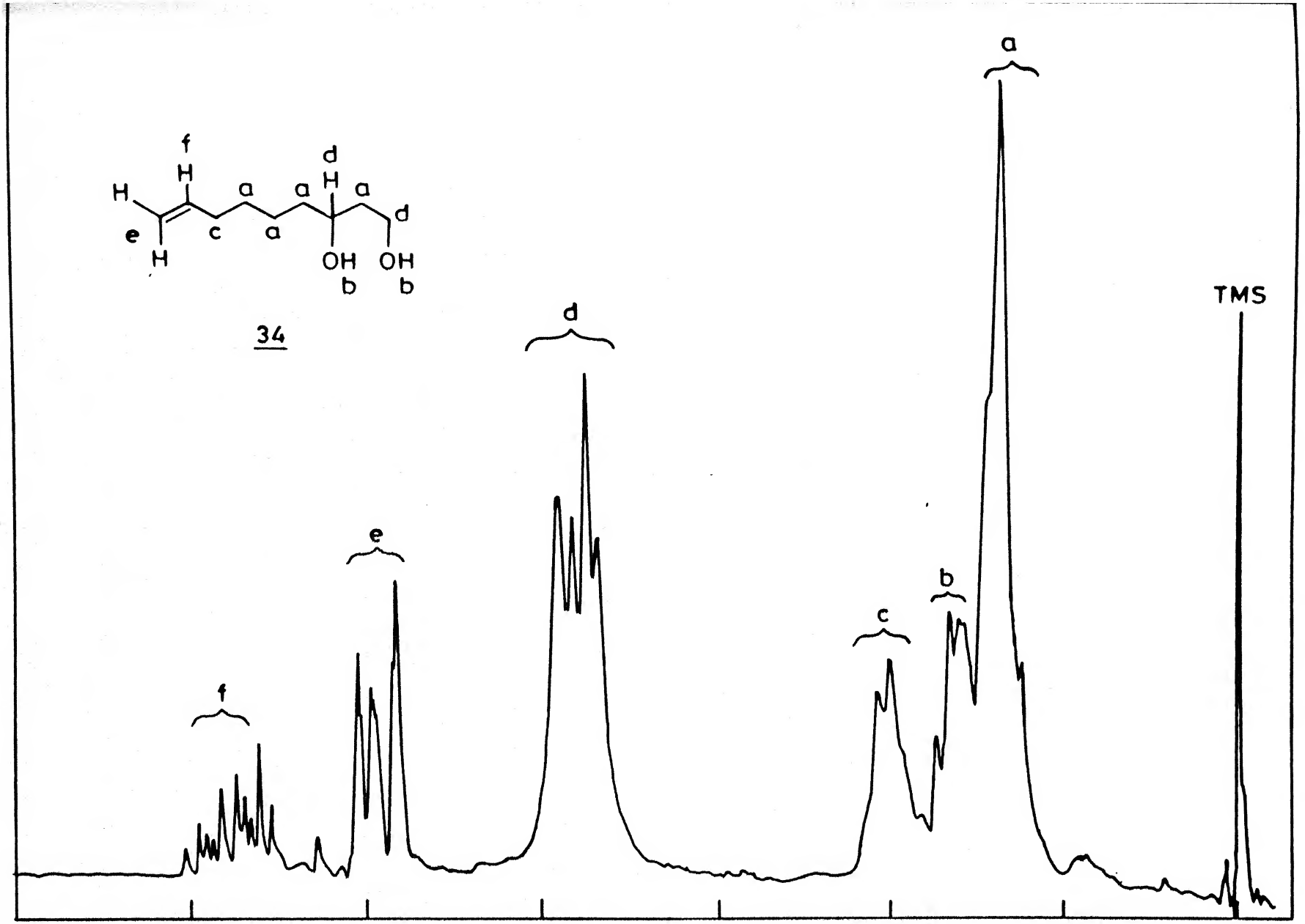
31 31a 32 33 34 35 36 37 α-lipoic acid



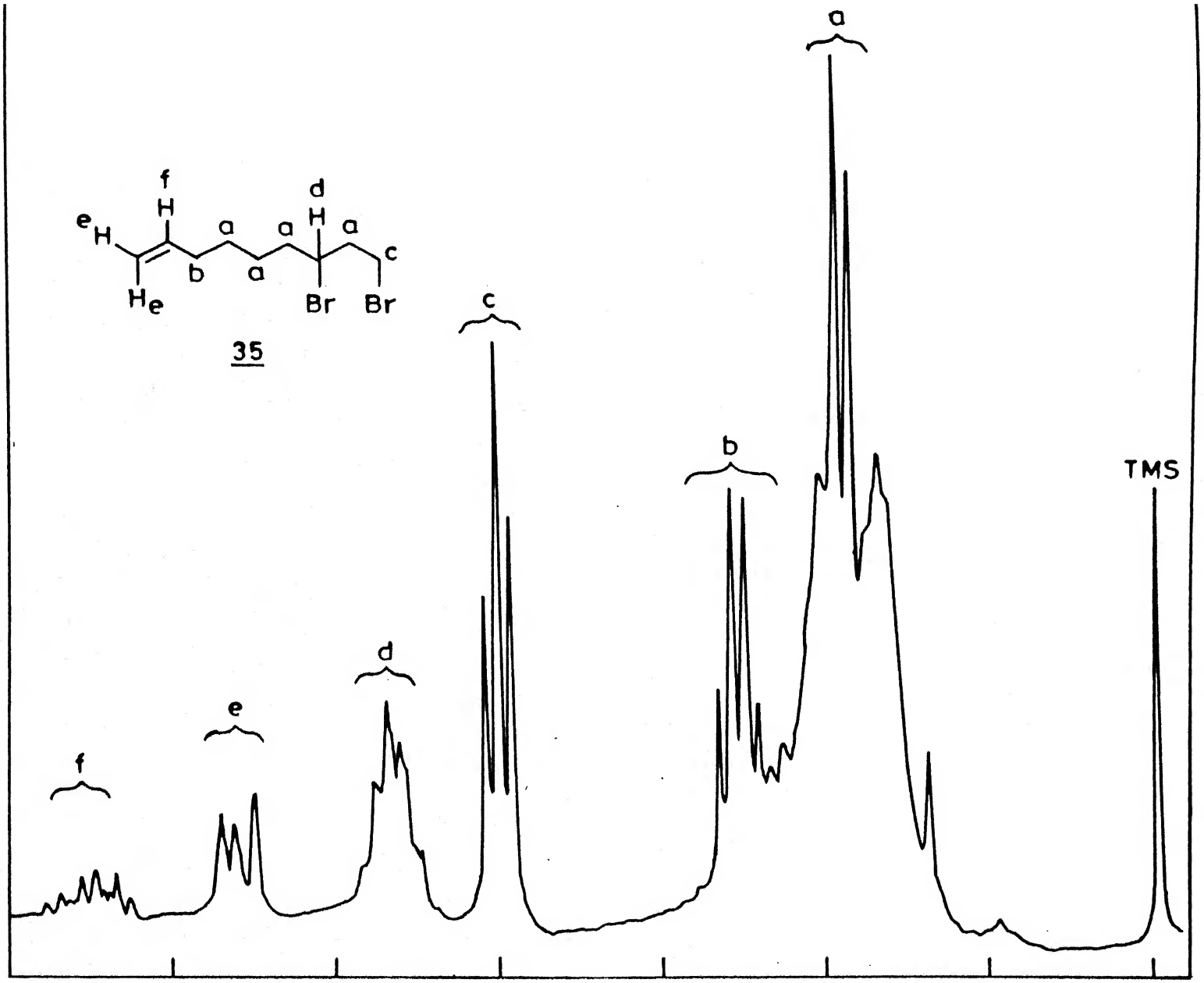
^{1}H NMR spectrum (80 MHz) of 32



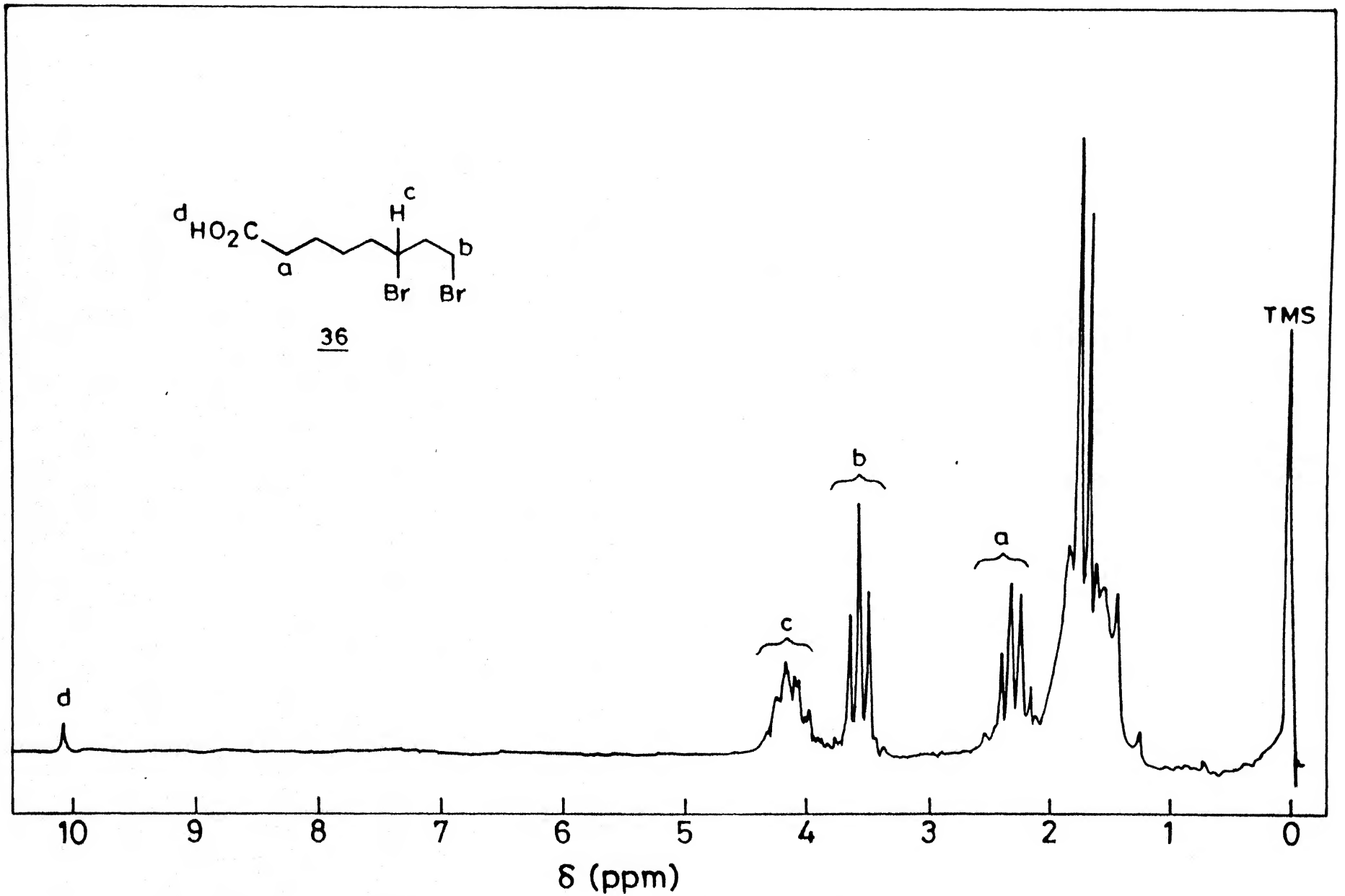
^{1}H NMR spectrum (80 MHz) of 33



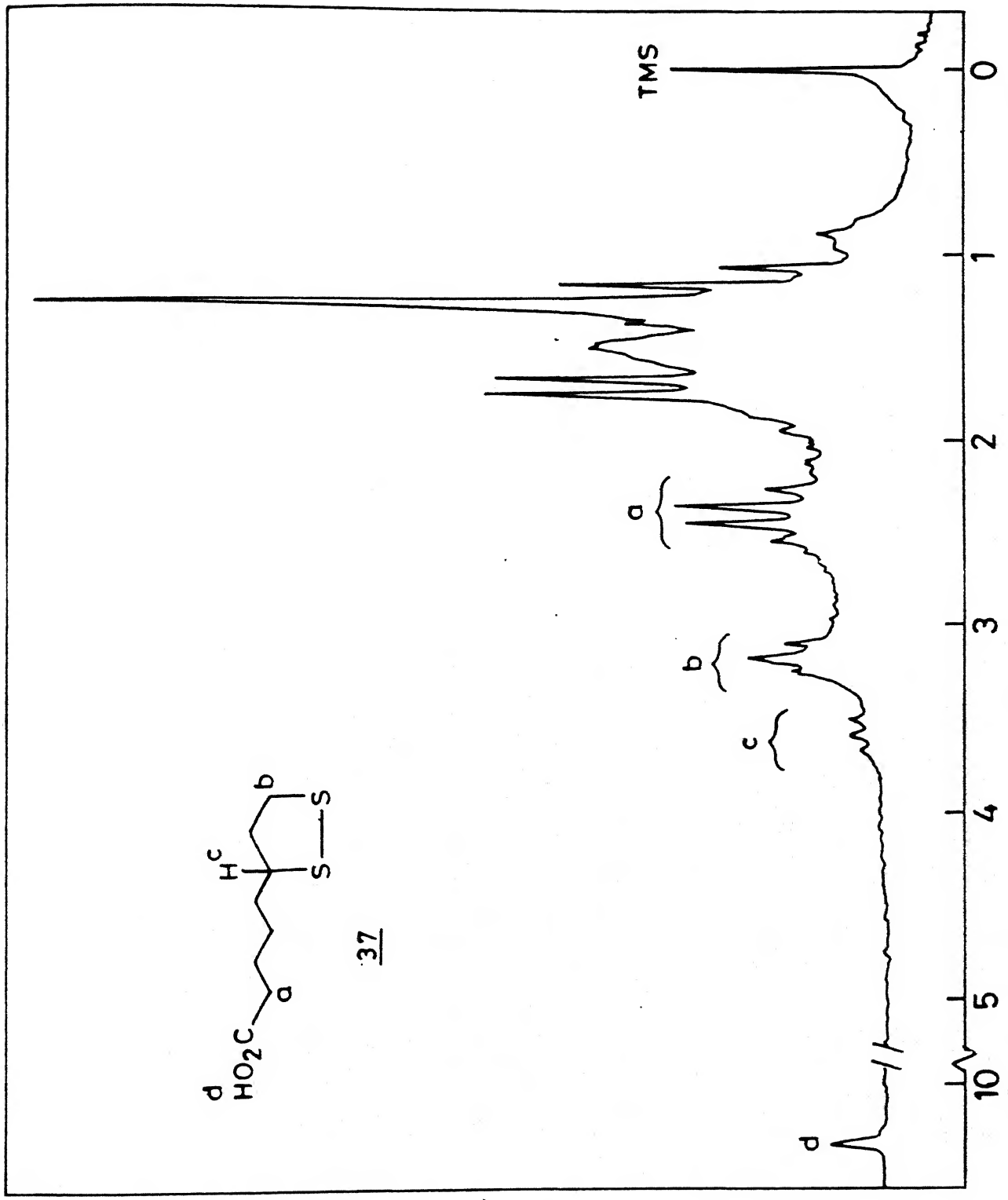
^{1}H NMR spectrum (80 MHz) of 34



^{1}H NMR spectrum (90 MHz) of 35



^{1}H NMR spectrum (80 MHz) of 36



^{1}H NMR spectrum (80 MHz) of 37

Alkylation of the dianion of acetoacetic ester **31a** with 5-bromo-1-pentene gave the keto ester **32** in 78% yield. **32** on reduction with $NaBH_4$ gave the corresponding hydroxy-ester **33** in 81% yield. The diol **34** was obtained (60%) by lithium aluminium hydride reduction of **33**. Diol **34** on treatment with PBr_3 gave the dibromide **35** in 56% yield. The dibromo olefin **35** was smoothly converted into the corresponding dibromo acid **36** in 84% yield by oxidation under heterogeneous conditions using $KMnO_4$-$CuSO_4.5H_2O$ reagent[47] in dichloromethane. The dibromo acid **36** was then reacted with piperidinium tetrathiotungstate **6** (DMF, 50 ^oC, 4h) to afford (±) α-lipoic acid **37** (65%), m.p. 45-47 ^oC. This compound exhibited spectral characteristics identical to those reported for α-lipoic acid in the literature.[48]

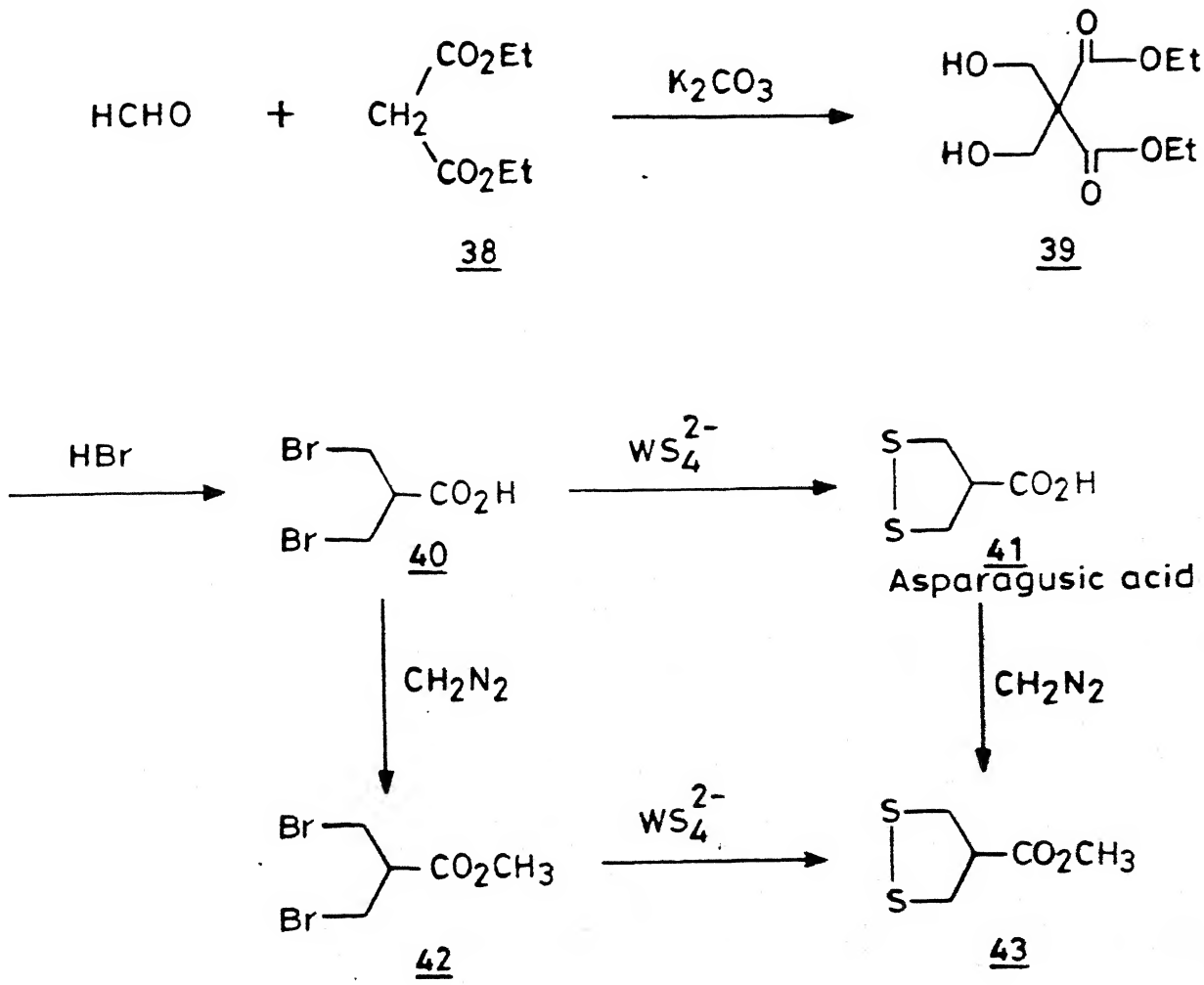
Synthesis of Asparagusic Acid **41**

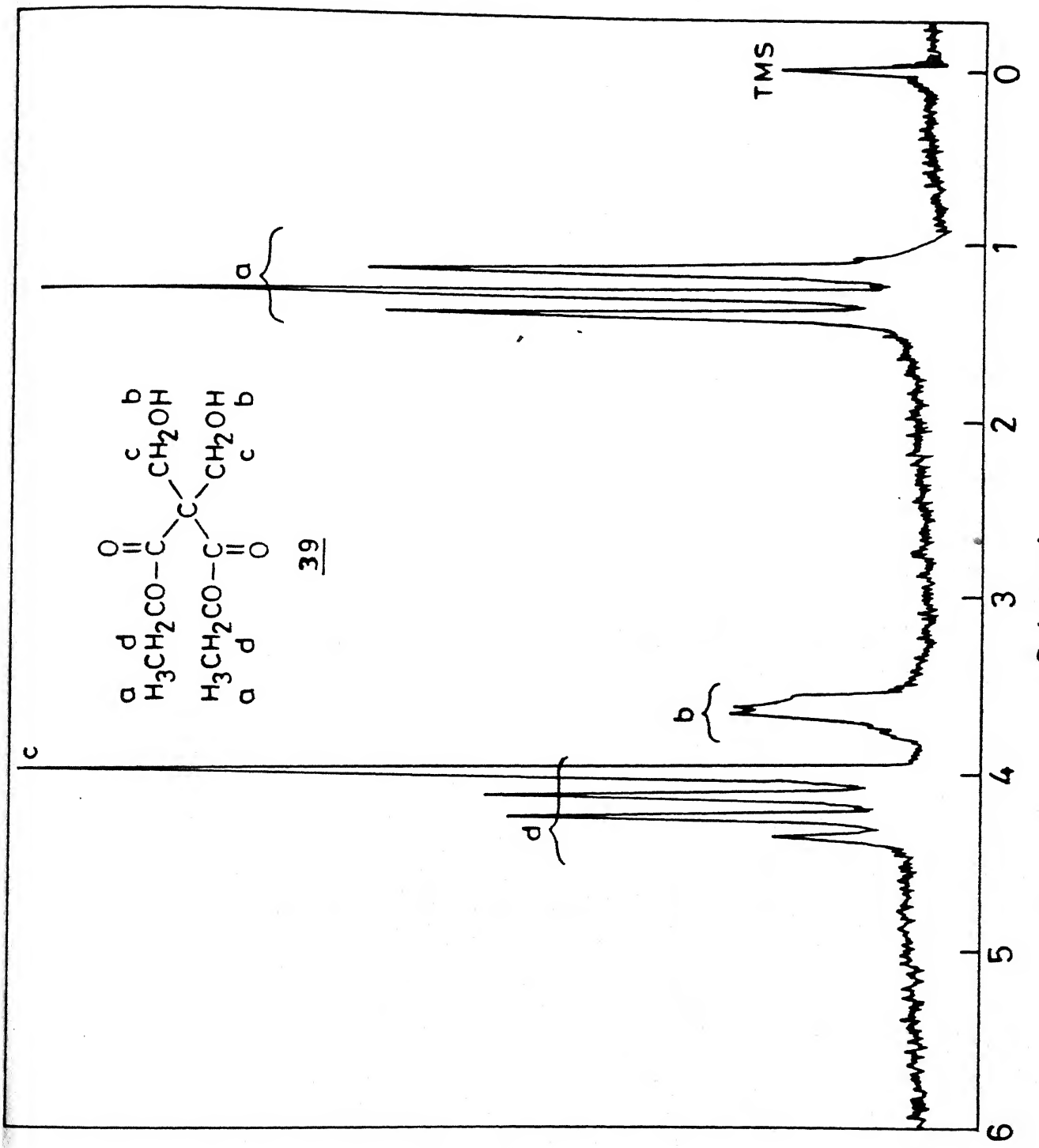
A short approach to the synthesis of asparagusic acid **41** is depicted in **Scheme 2.18**. Malonic ester **38** is an ideal starting material which in two steps can be converted to the dibromide **40**.[49] Application of the key reaction of tetrathiometallate **6** with **40** gave asparagusic acid **41** which was then converted to its methyl ester **43**[32] on treatment with diazomethane. The compound **43** was also obtained by treating dibromo ester **42** with **6**.

2.3 EXPERIMENTAL SECTION

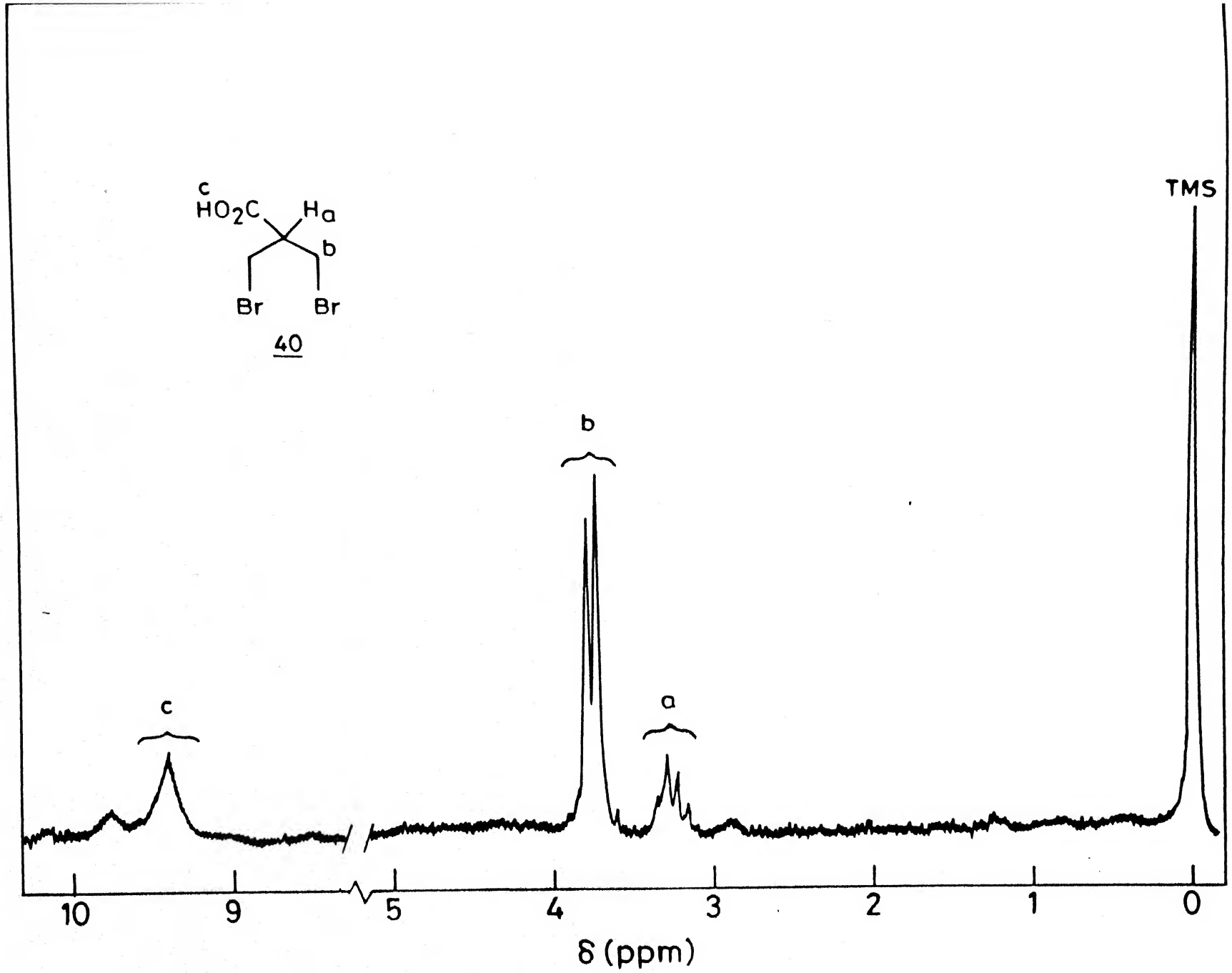
Experimental Procedure

Scheme 2.18

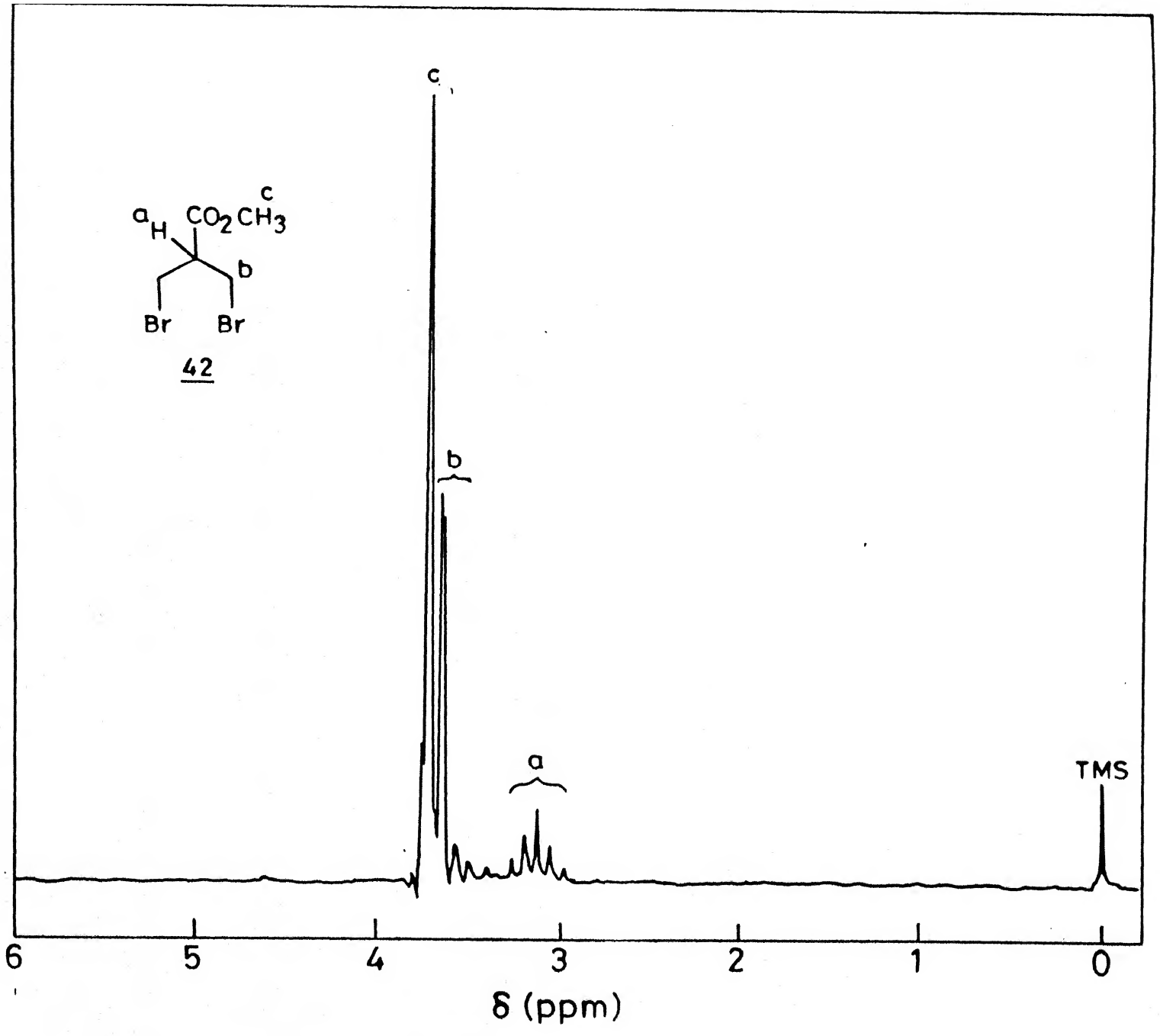

HCHO
+
CO2Et
CH2
CO2Et
K2CO3
HO
O
OEt
HO
OEt
O
38
39
HBr
Br
CO2H
Br
40
WS4 2-
S
CO2H
S
41
Asparagusic acid
CH2N2
CH2N2
Br
CO2CH3
Br
42
WS4 2-
S
CO2CH3
S
43



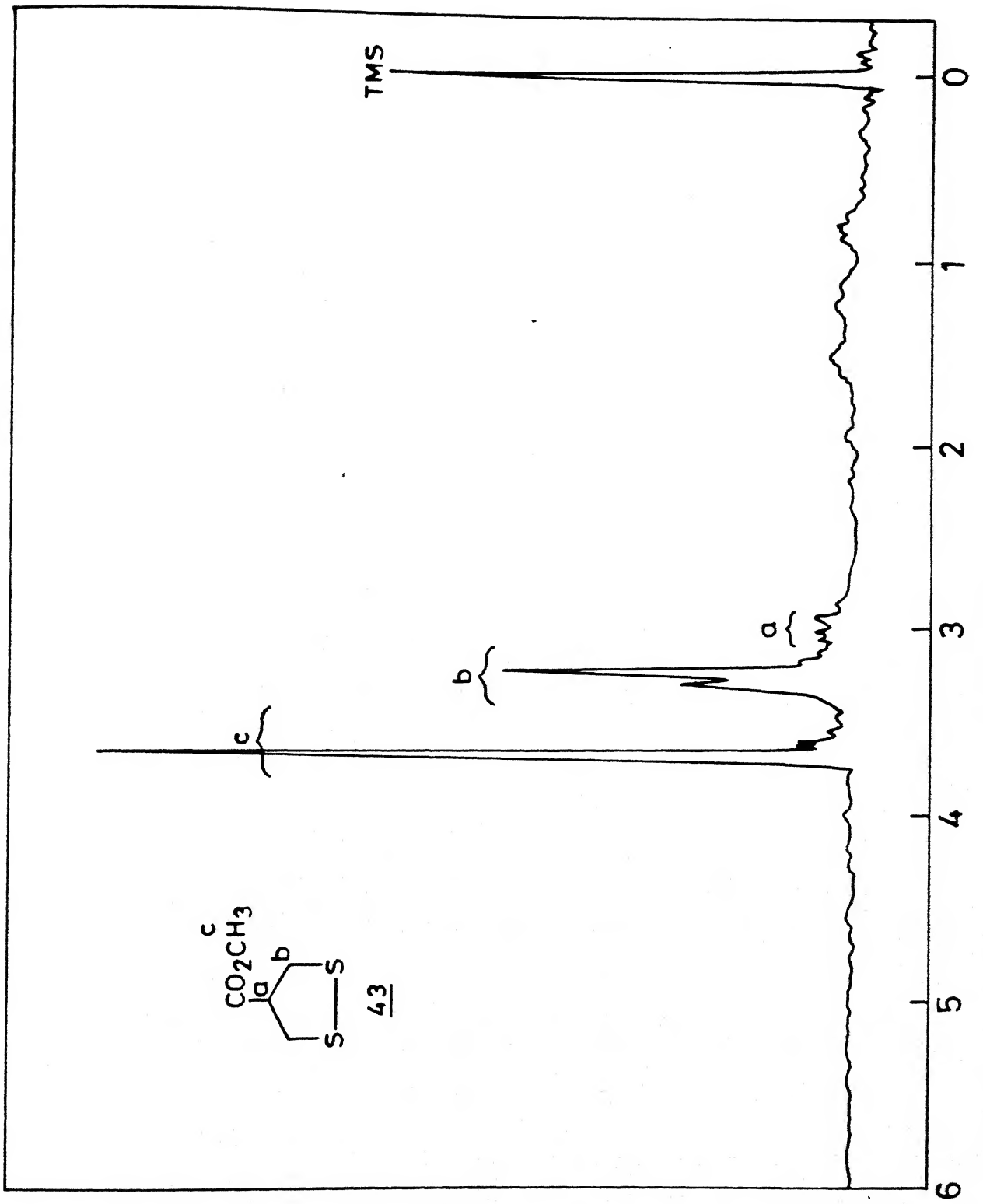
^{1}H NMR spectrum (60 MHz) of 39



^{1}H NMR spectrum (90 MHz) of 40



^{1}H NMR spectrum (80 MHz) of 42



^{1}H NMR spectrum (80 MHz) of 43

All the reactions were performed in oven dried apparatus. Reaction mixture were stirred magnetically unless otherwise specified and all the reactions were carried out in the dark. Reaction product solutions were concentrated using a Perfit rotary evaporator and products were characterized by comparison with authentic samples (spectra, T.L.C., m.p.). Lassaigne's test was performed on each compound for detection of sulfur

Materials

Commercial grade solvents were distilled prior to use. Dimethyl formamide was initially purified by azeotropic distillation with benzene. The residual solvent was shaken with calcium oxide, filtered and distilled at reduced pressure. The fraction having b.p. 76 ^{o}C/39 mm Hg was collected. The distillate was stored over a type 4 Å molecular sieve.

Chromatography

Analytical thin layer chromatography was performed on Merck precoated glass backed silica gel 60F-254 0.25 mm plates. Visualization of the spots was effected by one or more of the following techniques:(a) ultraviolet illumination; (b) exposure to iodine vapour; (c) immersion of the plate in a 10% solution of phosphomolybdic acid in ethanol followed by heating to ca. 200 ^{o}C.

Column chromatography was performed using 60-120 and 100-200 mesh Acme silica gel. The flash chromatography was performed using Merck thin-layer chromatography silica gel.

Physical Data

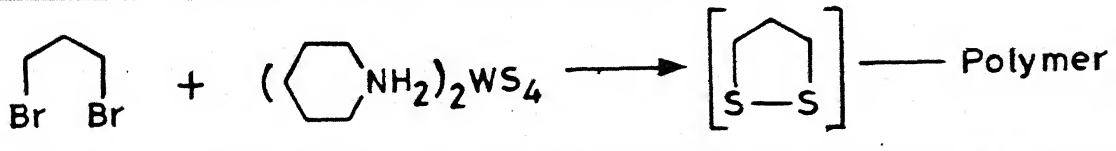
Melting points (m.p.) were determined with a uni-melt capillary melting point apparatus and are uncorrected. Boiling points (b.p.) are uncorrected.

Bulb to bulb distillation was carried out on a Büchi-GKR-50 distillation unit.

Infrared (IR) spectra were recorded on Perkin-Elmer model 1320 and 580 spectrophotometers and are reported in wave numbers (cm^{-1}).

Proton magnetic resonance (PMR) spectra were recorded at 90 MHz on a Varian EM-390 instrument, at 80 MHz on Bruker WP-80 instrument and at 90 MHz on Jeol FX-90Q instrument. Chemical shifts are reported in parts per million down field from internal reference tetramethyl silane (TMS) (δ). Multiplicity is indicated using the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad); etc. Mass spectra (MS) were recorded on a Jeol JMS D-300 mass spectrometer. Principal molecular fragments are reported.

Reaction of 1,3-Dibromopropane **4** with **6**



To a solution of piperidinium tetrathiotungstate **6** (1.936 g, 4 mmol) in dimethyl formamide (20 ml) was added dropwise with constant stirring 1,3-dibromopropane **4** in dimethyl formamide (5 ml). The reaction mixture was worked up after 2 h

by diluting it with water (150 ml) and extracting it with petroleum ether (40-60 °C) (4x15 ml). The organic extracts were washed with water, dried (anhydrous $MgSO_4$) amd concentrated to give a white polymerized material **5a**, m.p. 71-75 °C (lit.[39] m.p. 76 °C).

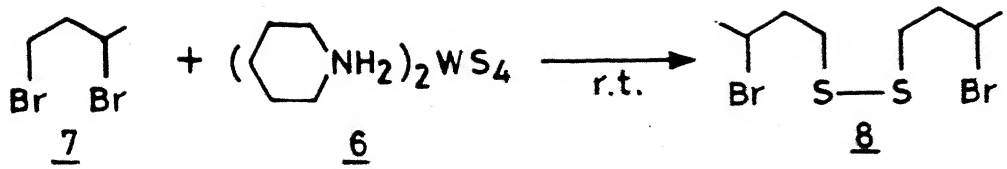
IR ($CHCl_3$) : 2955, 2875, 960, 880 cm^{-1}.

Preparation of 1,3-Dibromobutane **7**[4]

7

1,3-Dihydroxybutane (0.900 g, 10 mmol) and purified red phosphorus (0.21 g, 6.66 mmol) were placed in a three necked flask fitted with a reflux condenser and dropping funnel containing bromine (2.427 g, 15.15 mmol). The reaction mixture was heated such that contents refluxed gently, and then bromine was added in such a manner that very little bromine vapor was above the surface of the reaction mixture. After the addition was complete, reaction mixture was refluxed gently for 2 h. Reaction mixture was then filtered on a Büchner funnel and the crude bromide washed subsequently with water, dil. HCl, 10% sod. bicarbonate solution and finally with water. The product was dried (anhyd. $CaCl_2$) and concentrated to give 1,3-dibromobutane **7** (1.96 g, 91%), b.p. 71-72 °C/20 mm (lit.[38] b.p. 174-175 °C).

Reaction of 1,3-Dibromobutane **7** with **6** at room temperature



7 6 8

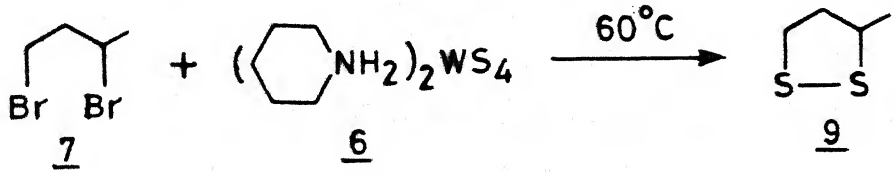
To a solution of piperidinium tetrathiotungstate **6** (1.936 g, 4 mmol) in dimethyl formamide (20 ml) was added dropwise with constant stirring 1,3-dibromobutane **7** (0.664 g, 4 mmol) in dimethyl formamide (5 ml) at ~28 °C. After stirring for 4 h at 28 °C, the reaction mixture was worked up as described previously. The crude product on chromatographic purification (10% ether/petroleum ether 60-80 °C) afforded the dimer **8** (0.363 g, 54%) as a pale yellow oil.

IR (thin film) : 2940, 2870, 1465, 1380, 970, 895 cm^{-1}.

^1H NMR (CCl_4) : δ 1.73 (d, 6 H); 2.13 (t, 4 H); 2.7-3.0 (m, 4 H); 4.07-4.3 (m, 2 H).

MS (m/e) : 338 (M^++4), 336 (M^++2), 334 (M^+).

Reaction of 1,3-Dibromobutane **7** with **6** at 60 °C



7 6 9

To a solution of piperidinium tetrathiotungstate **6** (1.936 g, 4 mmol) in dimethyl formamide (25 ml) was added dropwise with constant stirring 1,3-dibromobutane **7** (0.664 g, 4 mmol) in dimethyl formamide (10 ml) at ~60 °C. The resulting reaction mixture was stirred at 60 °C for 4 h. After the usual workup, the crude product was purified by flash chromatography on

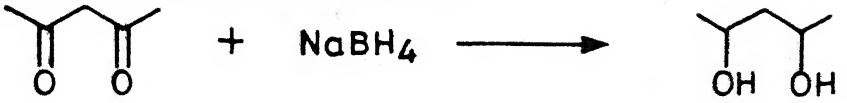
silica gel (1:5, ether/petroleum ether, 40-60 °C) to yield 3-methyl-1,2-dithiolane [37a] (0.301 g, 61%) as a pale yellow oil.

IR (thin film) : 2951, 2871, 1465, 1380, 970, 895 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.4 (d, 3 H); 1.9-2.3 (m, 2 H) and 3.0-3.4 (m, 3 H).

MS (m/e) : 120 (M^+), 88, 56.

Preparation of 2,4-Pentane diol



A solution of acetylacetone (28.5 g, 285 mmol) in methanol (85 ml) was added slowly to a stirred solution of sodium borohydride (7.14 g, 257 mmol) and sodium hydroxide (1.4 g) in water (71 ml), maintaining the temperature below -20 °C. After the addition was complete, the solvents were removed under reduced pressure to leave a colorless solid. Glycerol (113 ml) was added and distilled to yield 2,4-pentanediol (23 g, 77%), b.p. 86°C/ 6 mm (lit.[50] b.p. 98 °C/10 mm).

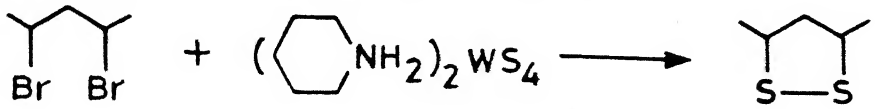
Preparation of 2,4-Dibromopentane 10

10

2,4-Dihydroxypentane (1.04 g, 10 mmol) and purified red phosphorus (0.21 g, 6.66 mmol) were placed in a three necked flask fitted with a reflux condenser and a dropping funnel containing bromine (2.427 g, 15.15 mmol). The reaction mixture

was heated such that contents refluxed gently and then bromine was added such that very little bromine vapor was above the surface of the reaction mixture. After the addition was complete, the reaction mixture was refluxed gently for 1 h. The crude bromide was subsequently washed with water, dil. HCl, water, 10% sodium bicarbonate solution and finally water. Product was dried (anhydrous $CaCl_2$) and concentrated to give 2,4-dibromopentane **10** (1.9 g, 82%), b.p. 62-63 °C/9 mm (lit.[42] b.p. 63.5 °C/9 mm).

Reaction of 2,4-Dibromopentane **10** with **6**



10 **6** **11**

To a solution of piperidinium tetrathiotungstate **6** (1.936 g, 4 mmol) in dimethyl formamide (20 ml) was added dropwise with constant stirring 2,4-dibromopentane **10** in dimethyl formamide (5 ml) at ~28 °C. The reaction mixture was worked up after 6 h. Chromatographic purification using 5% ether/petroleum ether (40-60 °C) as eluent gave 3,5-dimethyl-1,2-dithiolane **11**[39,43] (0.34 g, 64%) as a pale yellow oil.[2]

IR (thin film) : 2967, 2870, 1466, 1380, 1000-960, 890 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.12-1.22 (d, 6 H); 1.25-1.47 (m, 2 H); 3.06-3.47 (m, 2 H).

MS (m/e) : 134 (M^+), 90.

Preparation of 2,4-Ditosylpentane **12**

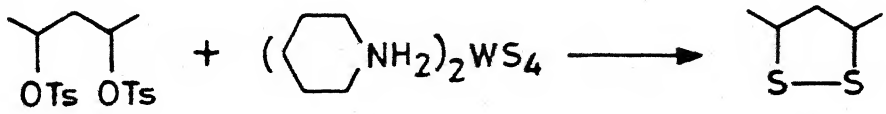
12

2,4-Pentane diol (1.04 g, 10 mmol) was taken in dry dichloromethane (15 ml) and to it was added dry triethylamine (2.0 g, 20 mmol). Tosyl chloride (3.813 g, 2.2 mmol) was added in portions with constant stirring. The reaction mixture was allowed to stir for 24 h at 0 °C and then it was washed successively with water, cold dilute hydrochloric acid, water saturated aq. sodium-bicarbonate and then water and dried over anhydrous $MgSO_4$. The dichloromethane was removed under reduced pressure to give **12**[1b] (3.94 g, 91%).

IR (thin film) : 3060-3010, 2960, 2865, 1470, 1380, 1180, 733, 660 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.22-1.26 (d, 6 H); 1.29-1.34 (m, 2 H); 2.5 (s, 6 H); 4.40-4.84 (m, 2 H); 7.34-7.46 (d, 4 H); 7.87 (d, 4 H).

Reaction of **12** with **6**

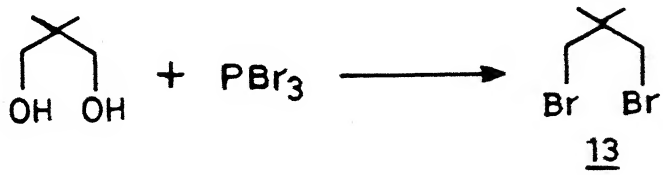


12 6 11

To a solution of piperidinium tetrathiotungstate **6** (0.484 g, 1 mmol) in dimethyl formamide (20 ml) was added **12** (0.432 g, 1 mmol) in dimethyl formamide (5 ml) with constant stirring. It was worked up after 12 h as described earlier and chromatographic purification using 5% ether/petroleum ether (60-80 °C) as eluent gave **11** (0.073 mg, 54%) and starting material **12**

(0.013 mg, 9%). Spectral data were found to be identical with that of compound **11** prepared by the other route.

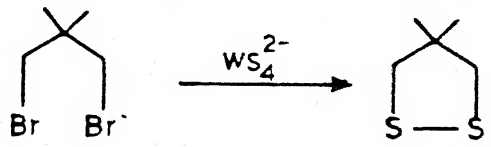
Preparation of 2,2-Dimethyl-1,3-dibromopropane **13**



13

In a three necked flask fitted with a reflux condenser and a dropping funnel was placed 2,2-dimethyl-1,3-propane diol (2.08 g, 20 mmol). To this was added phosphorus tribromide (1.712 g, 6.28 mmol) from the dropping funnel over a period of 0.5 h. The reaction mixture was heated at 115 ^{o}C for 4 h. After the usual workup 2,2-dimethyl-1,3-dibromopropane **13**[40] was obtained as a colorless liquid (2.78 g, 60%), b.p. 184-86^{o}C (lit.[40] b.p. 185-190 ^{o}C).

Reaction of 2,2-Dimethyl-1,3-dibromopropane **13** with **6**



To a solution of piperidinium tetrathiotungstate **6** (1.936 g, 4 mmol) in dimethyl formamide (20 ml), compound **13** (0.920 g, 4 mmol) in dimethyl formamide (5 ml) was added dropwise with constant stirring. The reaction was over in 6 h. It was worked up the same way as described earlier. After the usual work-up, the crude product was purified by flash chromatography on silica gel (1:10, ether/petroleum ether, 40-60 ^{o}C) to give

14[41] (0.364 g, 68%).

IR (thin film) : 2950, 2870, 1385, 1365, 970, 895 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.18 (s, 6 H); 2.78 (s, 4 H).

Preparation of **15**

15

The diol (0.158 g, 1 mmol) was taken in dry dichloromethane (10 ml) and to it was added dry triethylamine (0.2 g, 2 mmol). Tosyl chloride (0.381 g, 2.2 mmol) was added in portions with constant stirring. The reaction mixture was allowed to stir at 0 °C for 24 h. The reaction mixture was worked up, as described earlier and the crude product on chromatographic purification using 10% ether/petroleum ether (60-80 °C) gave the compound **15** (0.542 g, 97%).

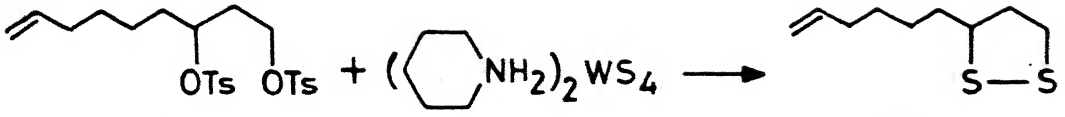
IR (thin film) : 3080, 2950, 2920, 2870, 2860, 1640, 1360, 1190, 620 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.1-1.6 (m, 8 H); 1.66-1.93 (m, 2 H); 2.43 (s, 6 H); 3.73-4.03 (t, 2 H); 4.36-4.63 (m, 1 H); 4.96-5.06 (m, 2 H); 5.33-5.90 (m, 1 H); 7.03-7.36 (d, 4 H); 7.46-7.7 (d, 4 H).

Anal. Calcd for $C_{23}H_{30}O_6S_2$: C, 59.22; H, 6.44.

Found : C, 59.27; H, 6.46.

Reaction of compound **15** with **6**



15 **6** **16**

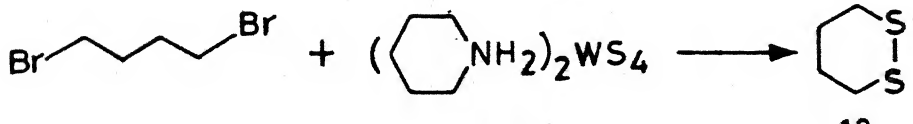
To a solution of piperidinium tetrathiotungstate **6** (0.242 g, 0.5 mmol) in dimethyl formamide (10 ml) was added dropwise with constant stirring compound **15** (0.233 g, 0.5 mmol) in dimethyl formamide (2 ml). The reaction mixture was worked up after 12 h as described earlier. Chromatographic purification using 15% ether/petroleum ether (40-60 ^{o}C) as eluent gave the corresponding dithiolane **16** (0.051 g, 54%) as a pale yellow oil.

IR (thin film) : 3080, 1640, 1500, 1100 cm^{-1}.

^{1}H NMR ($CDCl_3$) : δ 1.04-1.30 (m, 8 H); 1.68-1.96 (m, 2 H); 2.72-2.88 (m, 2 H); 3.0-3.36 (m, 1 H); 4.32-4.64 (m, 2 H); 5.0-5.44 (m, 1 H).

MS (m/e) : 188 (M^{+}), 124.

Reaction of 1,4-Dibromobutane **17** with **6**



17 **6** **18**

To a solution of piperidinium tetrathiotungstate **6** (1.936 g, 4 mmol) in dimethyl formamide (20 ml) was added with constant stirring 1,4-dibromobutane **17** (0.864 g, 4 mmol) in dimethyl formamide (5 ml). The reaction was over in 3 h. It

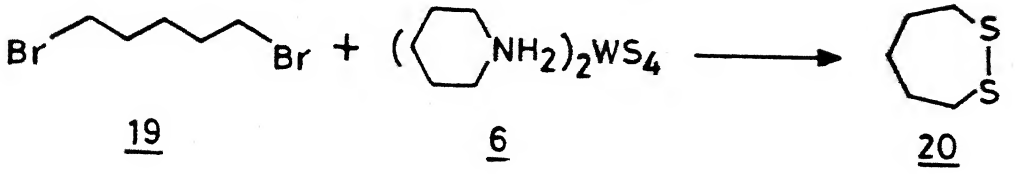
was worked up as described previously and chromatographic purification using 10% ether/petroleum ether (40-60 °C) as eluent gave 1,2-dithiane **18** (0.356 g, 74%), m.p.27-30 °C (lit.[4] m.p. 32- 33 °C).

IR ($CHCl_3$) : 2910, 1450, 1280, 745 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.95 (s, 4 H); 2.8 (s, 4 H).

MS (m/e) : 120 (M^+), 88.

Reaction of 1,5-Dibromopentane **19** with **6**



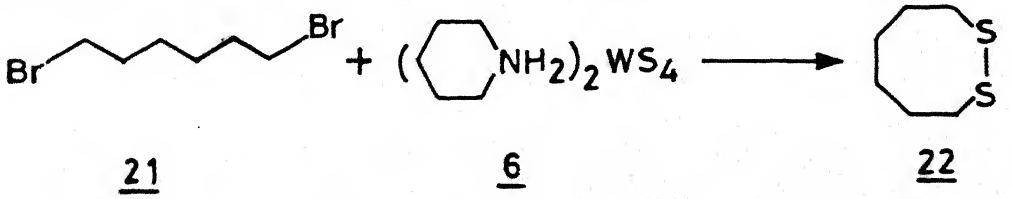
19 **6** **20**

To a solution of piperidinium tetrathiotungstate **6** (1.936 g, 4 mmol) in dimethyl formamide (20 ml) was added dropwise with constant stirring 1,5-dibromopentane **19** (0.920 g, 4 mmol) in dimethyl formamide (5 ml). After stirring for 5 h it was worked up as described earlier and chromatographic purification using 10% ether/petroleum ether (40-60 °C) as eluent gave compound **20**(0.270 g, 50%), b.p. 55-60 °C/1.7 mm (lit.[4,44] b.p. 41°C/2 mm).IR ($CHCl_3$) : 2910, 1450, 1280, 770 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.73-2.06 (m, 6 H); 2.8 (t, 4 H).

MS (m/e) : 134 (M^+), 102, 70.

Reaction of 1,6-Dibromohexane **21** with **6**



21 **6** **22**

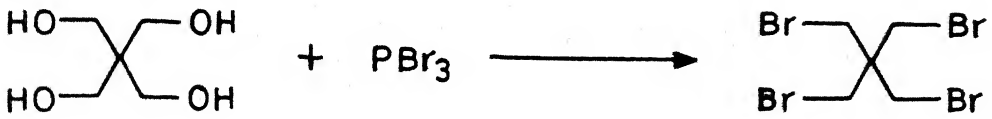
To a solution of piperidinium tetrathiotungstate **6** (1.936 g, 4 mmol) in dimethyl formamide (20 ml) was added dropwise with constant stirring 1,6-dibromohexane **21** (0.976 g, 4 mmol) in dimethyl formamide (5 ml). The reaction was allowed to stir at ~28 °C for 8 h. After the usual work-up, the crude product on chromatographic purification on silica gel, using 10% ether/petroleum ether (40-60 °C) as eluent gave 1,2-dithiaoctane **22**[44] (0.272 g, 46%), b.p. 60-63 °C/1 mm (lit.[44] b.p. 65.5 °C/2 mm).

IR ($CHCl_3$) : 2910, 1450, 770 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.53-1.88 (m, 8 H); 2.56 (t, 4 H).

MS (m/e) : 148 (M^+), 147, 115, 83.

Preparation of Tetrabromopentaerythritol **23**

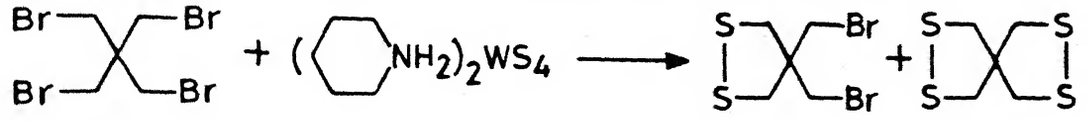


23

Pentaerythritol (1.25 g, 9.2 mmol) was placed in a round bottomed flask provided with a reflux condenser and a dropping funnel containing phosphorus tribromide (1.75 ml, 18.5 mmol). The flask was heated on a steam bath and phosphorus tribromide continuously added. When the addition was complete, steam bath was replaced by oil bath and the temperature was gradually raised to 170-180 °C. After heating at this temperature for 20 h, the orange-red reaction mixture was transferred to a beaker containing cold water (10 ml) and stirred thoroughly to reduce the lumps to smaller size. The red, flocculent material was

filtered with suction and washed several times with hot water. Finally it was washed with cold ethanol (2 ml, 95%). After drying, the material was transferred to a large soxhlet extractor and extracted exhaustively with 95% alcohol. The pentaerythrityl tetrabromide **23** separated from the alcohol and after cooling was collected by filtration, m.p. 159-61°C (lit.[45] m.p. 163°C).

Reaction of Pentaerythrityl tetrabromide **23** with **6**



23 **6** **24a** **24**

To a solution of piperidinium tetrathiotungstate **6** (1.936 g, 5 mmol) in dimethyl formamide (12 ml) was added with constant stirring pentaerythrityl tetrabromide **23** (0.776 g, 2 mmol) in dimethyl formamide (5 ml). The reaction was allowed to go for 12 h. It was worked up in the same manner as described earlier. Chromatographic purification using 25% ether/petroleum ether (40-60 °C) afforded the compound **24** (0.221 g, 55%), m.p. 69-70 °C (lit.[35] m.p. 70 °C) and compound **24a** (0.051, 13%) as an oil along with some starting material **23** (6%).

Compound 24

IR ($CHCl_3$) : 2955, 2875, 960, 880 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 3.18 (s, 8 H).

MS (m/e) : 196 (M^+), 164, 132, 117, 99, 85.

Compound 24a

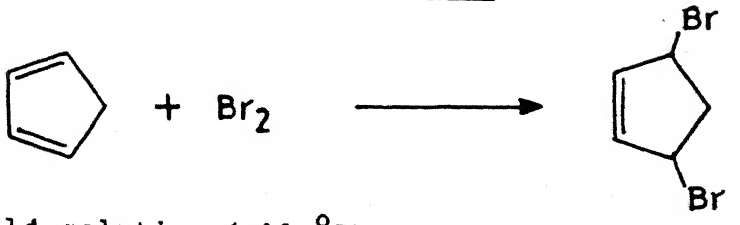
IR (thin film) : 2955, 2920, 2875, 2854, 970, 890 cm^{-1}.

^{1}H NMR ($CDCl_3$) : δ 3.18 (s, 4H); 3.53 (s, 4 H).

Anal. Calcd for $C_5H_8Br_2S_2$: C, 20.55; H, 2.74.

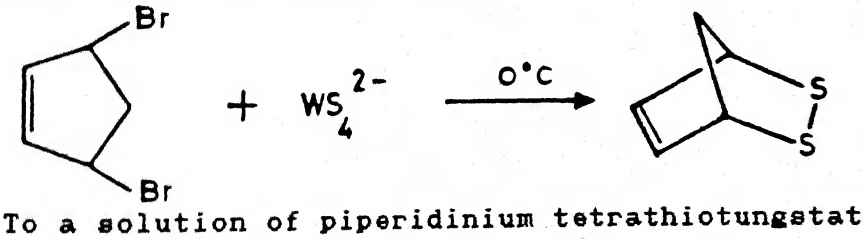
Found : C, 20.61; H, 2.75.

Preparation of 3,5-Dibromocyclopentene **25**



To a cold solution (-30 °C) of freshly distilled cyclopentadiene (6.6 g, 0.1 mol) in hexane (15 ml), bromine (16 g, 0.1 mol) was added dropwise with vigorous stirring. The trans isomer crystallized on the walls of the reaction vessel and was separated by decantation and recrystallized from ether to give a white, crystalline product (4.52 g, 20%), m.p. 43-44 °C (lit. m.p. 45 °C). The cis-isomer was obtained by evaporation of the n-hexane mother liquor and distillation of the residue at reduced pressure. In this manner, a colorless, constant boiling liquid was obtained (2.74 g, 12%), b.p. 52-54 °C/2.5 mm (lit.[37b] b.p. 53-55 °C/2.5 mm).

Reaction of 3,5-Dibromocyclopentene **25** with **6**



To a solution of piperidinium tetrathiotungstate **6** (1.936 g, 4 mmol) in dimethyl formamide (20 ml) at 0 °C was added dropwise with constant stirring 3,5-dibromocyclopentene **25**

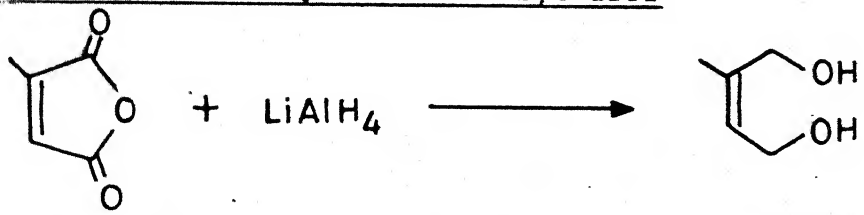
(0.904 g, 4 mmol) in dimethyl formamide (5 ml). The reaction mixture was stirred at 0 °C for 12 h. It was worked up by diluting the reaction mixture by water (100 ml) and extracting it with petroleum ether (40-60 °C) (4x15 ml). The organic layer was washed with water till the aqueous washings were almost colorless. Organic layer was dried (anhyd. $MgSO_4$) and concentrated. Chromatographic purification using pentane gave 1,2-dithianorborene 26 (0.102 g, 20%) as a white waxy solid which was found to be very unstable.

IR ($CHCl_3$) : 3010, 1660 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 2.47 (s, 1 H); 2.81 (s, 1 H); 4.17-4.3 (br,s 2 H); 5.68 (s, 2 H).

MS (m/e) : 130 (M^+).

Preparation of 2-Methylbut-2-ene-1,4-diol



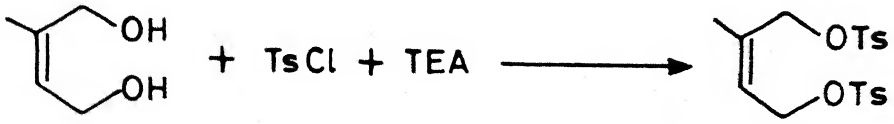
To a slurry of lithium aluminium hydride (2.489 g, 65.5 mmol) in dry THF (40 ml) at 0 °C was added dropwise with stirring citraconic anhydride[51] (2.8 g, 25 mmol) in dry THF (50 ml). After the addition was complete, the reaction mixture was refluxed for 48 h, cooled to 0 °C and worked up by careful addition of water (2.5 ml), 15% aq. NaOH (2.5 ml) and water (2.5x3 ml) and stirred for additional 15 min. It was filtered through a sintered funnel, washed with ether, the filtrate dried (anhyd. $MgSO_4$) and concentrated to give the crude allylic

diol. Chromatographic purification using 40% ethyl acetate/ petroleum ether (60-80 °C) as eluent gave pure diol (1.22 g, 48%).

IR ($CHCl_3$) : 3460, 3010, 2870, 1640 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 2.03 (s, 3 H); 3.92-4.42 (m, 4 H); 4.48 (br,s, 2 H); 5.44 (d, 1 H).

Preparation of the Ditosylate 27



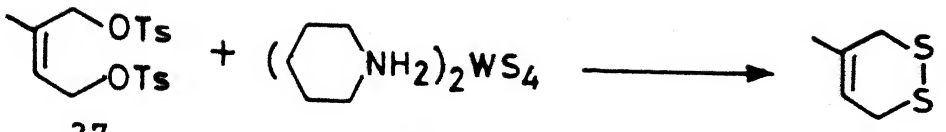
27

To a stirred solution of the diol (0.51 g, 5 mmol) in dichloromethane (10 ml) was added triethylamine (1.0 g, 10 mmol). The solution was cooled to 0 °C and to it was added in portions tosyl chloride (1.907 g, 1.1 mmol). The reaction mixture was allowed to stir at room temperature for 24 h. It was worked up as described previously. The crude product on chromatographic purification using 40% ethyl acetate/petroleum ether (60-80 °C) as eluent gave the ditosylate 27 (1.270 g, 62%).

IR ($CHCl_3$) : 3080, 2970, 1640, 1340, 1170 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.72 (s, 3 H); 2.4 (s, 6 H); 3.90-4.23 (m, 4 H); 5.07-5.32 (t, 1 H); 7.28-7.37 (d, 4 H); 7.71-7.81 (d, 4 H).

Reaction of Ditosylate 27 with 6



27 6 28

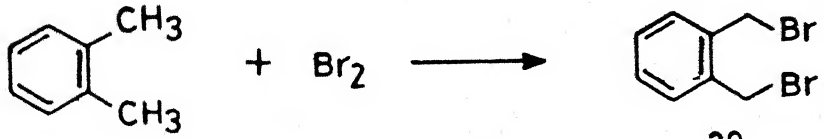
To a stirred solution of piperidinium tetrathiotungstate (0.484 g, 1 mmol) in dimethyl formamide (10 ml) was added dropwise the ditosylate **27** (0.410 g, 1 mmol) in dimethyl formamide (10 ml). The reaction was allowed to go for 18 h. It was worked up as described previously. Chromatographic purification using ether/petroleum ether (60-80 °C) gave **28** (0.057 g, 43%).

IR ($CHCl_3$) : 3010, 2970, 1600 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.72 (s, 3 H); 3.10-3.14 (m, 4 H); 5.06-5.31 (t, 1 H).

MS (m/e) : 132 (M^+).

Preparation of o-Xylene dibromide **29**

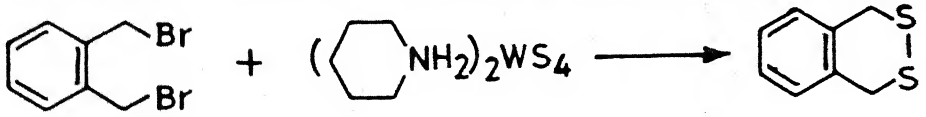


29

In a three necked flask, fitted with a dropping funnel and reflux condenser was placed o-xylene (1.06 g, 10 mmol). This was heated in an oil-bath and illuminated with a lamp (275 watt), When the temperature of the oil-bath reached 125 °C, the dropwise addition of bromine (3.52 g, 22 mmmol) was commenced with stirring. The rate of addition was regulated such that the entire bromine was added in 0.5 h. The mixture was stirred at 125 °C under illumination for an additional 0.5 h. It was then allowed to cool to 60 °C and poured into petroleum ether (60-80 °C) (10 ml). As the homogeneous solution cooled slowly

to room temperature, it was stirred frequently to prevent caking of the brown crystalline product that separated out. The product **29** was then separated by suction filtration, washed twice with cold petroleum ether (60-80 °C) (25 ml) and then dried on filter paper until nearly dry. Final drying was effected in vacuum desiccator containing solid KOH. The product **29** was obtained as a brown solid (1.23 g, 48% yield), mp. 89-91 °C (lit.[36b] m.p. 93- 94 °C).

Reaction of **29** with Piperidinium tetrathiotungstate **6**



29 **6** **30**

To a solution of piperidinium tetrathiotungstate **6** (1.936 g, 4 mmol) in dimethyl formamide (20 ml) was added dropwise with constant stirring, o-xylene dibromide **29** (1.056 g, 4 mmol) in dimethyl formamide (5 ml) at room temperature(~28 °C). The reaction took 4 h to go to completion. It was worked up by diluting the reaction mixture with water (150 ml) and extracting it with ether (4x30 ml). The ether extracts were washed several times with water till the aqueous washings were almost colorless. The organic layer was dried (anhydrous $MgSO_4$) and concentrated under reduced pressure. Chromatographic purification using pentane as eluent gave compound **30** (0.632 g, 94%), m.p. 78-79 °C (lit.[36c] m.p. 80°C).

IR (KBr) : 3060, 2960, 1600 cm^{-1}.

^1H NMR (CCl_4) : δ 4.03 (s, 4 H); 7.08 (br,s, 4 H).

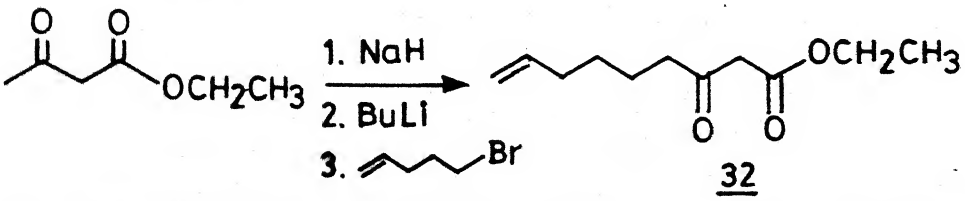
MS (m/e) : 168 (M^+), 136, 104.

Lipoic Acid 37

Preparation of 5-Bromo-1-pentene

1,5-Dibromopentane (12.82 g, 55.74 mmol) with freshly distilled hexamethyl phosphoric triamide (10 g, 55.8 mmol) was heated to 200-210 °C (bath temperature under dry atmosphere). The product that distilled out below 130 °C was collected. It was further fractionally distilled to get 5-bromo-1-pentene (7.97 g, 96%), b.p. 127-128 °C/atm. (lit.[52] b.p. 128 °C/atm.).

Preparation of **32**



32

Dry THF (50 ml) was taken in a three necked round bottom flask containing NaH (1.08 g, 22 mmol). The flask was stoppered with a septum cap, flushed with nitrogen and cooled on ice. Then acetoacetic ester **31** (2.6 g, 20 mmol) was added dropwise and the colorless solution was stirred at 0 °C for 20 minutes. To this solution was added dropwise 1.6 M BuLi (13.2 ml, 21 mmol) in hexane and the yellow solution of the dianion **31a** was stirred at 0 °C for an additional 0.5 h before using. To the solution of 20 mmol of the dianion in dry THF (50 ml) prepared as above, pentenyl bromide (3.28 g, 22 mmol) in dry THF (4 ml) was added. This reaction mixture was then slowly allowed to warm upto room temperature (~28 °C) and stirred for

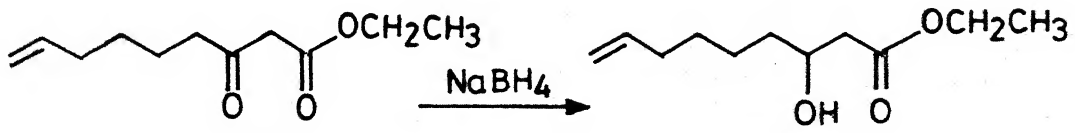
additional 3 h. This was quenched with conc. HCl (4 ml) in H_2O (10 ml) and ether (30 ml). The organic layer was separated and the aqueous layer was further extracted with ether (3x15 ml). The extracts were combined, washed with water until neutral, dried (anhyd. $MgSO_4$) to give the alkylated product **32** (3.101 g, 78%) as a liquid.

IR (thin film) : 3090, 1735, 1715, 1640 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.22-1.41 (t, 3 H); 1.47-1.66 (m, 4 H); 1.97-2.22 (m, 2 H); 2.5-2.66 (t, 2 H); 3.47 (s, 2 H); 4.09-4.38 (q, 2 H), 4.88-5.19 (m, 2 H); 5.63-6.13 (m, 1 H).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.67; H, 9.09.
Found : C, 66.71; H, 9.10.

Reduction of compound **32**



32 **33**

The keto ester **32** (1.98 g, 10 mmol) was dissolved in distilled ethanol (15 ml) and sodium borohydride (0.38 g, 10 mmol) was added in portions at 0 °C. The mixture was then stirred for 1 h at 0 °C and allowed to warm upto room temperature (~28 °C) and stirred for another 3 h. Cold water (30 ml) was added and reaction mixture was allowed to stir for an additional 1 h. This was then extracted with chloroform (4x20 ml). The organic layer was washed with brine, dried (anhyd. $MgSO_4$) and concentrated to give compound **33** (1.609, 81%) as an

oil.

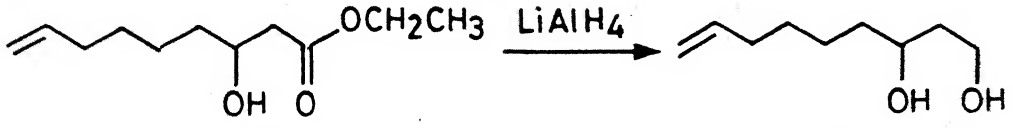
IR ($CHCl_3$) : 3360, 3080, 1735, 1640 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.15-1.34 (t, 3 H), 1.34-1.53 (br,s, 6 H), 1.87-2.18 (m, 2 H), 2.31-2.5 (m, 2 H); 3.18 br,s, 1 H); 3.81-4.28 (m, 3 H); 4.75-5.09 (m, 2 H); 5.46-6.03 (m, 1 H)

Anal. Calcd for $C_{11}H_{20}O_3$: C, 66.00; H, 10.00.

Found : C, 66.04; H, 9.98.

Preparation of compound **34**



33 34

To a slurry of lithium aluminium hydride (0.35 g, 9.2 mmol) in dry tetrahydrofuran (5 ml) was added dropwise with stirring compound **33** (1.84 g, 9.2 mmol) in dry THF (10 ml). After the addition was complete the mixture was refluxed with stirring for 8 h, cooled to 0 ^oC with ice and worked up by careful addition of water (0.35 ml), 15% aqueous sodium hydroxide (0.35 ml) and water (1.05 ml) and stirred for an additional 15 minutes. It was filtered through a sintered funnel and washed with ether. The filtrate was dried (Na_2SO_4) and concentrated to give **34** (0.866 g, 60%) as an oil.

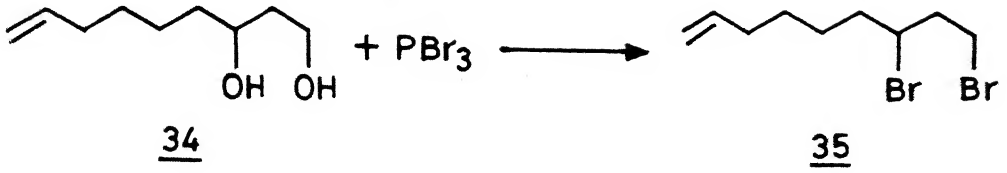
IR (thin film) : 3450, 3060, 1640 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.25-1.5 (m, 8 H); 1.54-1.75 (m, 2 H); 1.84-2.18 (m, 2 H); 3.53-3.96 (m, 3 H); 4.71-5.06 m, 2 H); 5.43-6.03 (m, 1 H).

Anal. Calcd for $C_9H_{18}O_2$: C, 68.35; H, 11.39.

Found : C, 68.42; H, 11.40.

Preparation of compound **35**



34 **35**

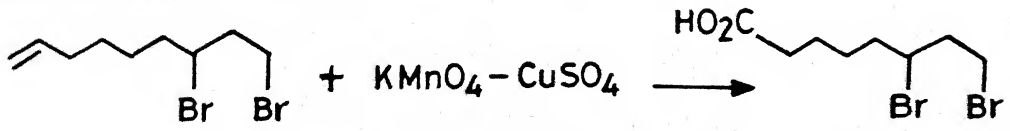
In a three necked flask fitted with a reflux condenser and a dropping funnel was placed compound **34** (0.632 g, 4 mmol). To this was added phosphorus tribromide (0.338 g, 1.25 mmol) from the dropping funnel over a period of 1 h. The temperature was not permitted to rise above ~60 °C. It was allowed to stir at 28 °C for 5 h and refluxed gently for 1 h. It was worked up the same way as described earlier. Concentration of the solvent afforded compound **35** (0.634 g, 56%).

IR (thin film) : 3010, 2860, 1650 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.22-1.76 (m, 8 H); 1.9-2.14 (q, 2 H), 3.43-3.68 (t, 2 H); 3.93-4.28 (m, 1 H); 4.71-5.06 (m, 2 H); 5.43-6.03 (m, 1 H).

MS (m/e) : 286 (M^++4), 284 (M^++2), 282 (M^+).

Preparation of compound **36**



35 **36**

Potassium permanganate (4 g), copper sulfate (2 g) and water (0.2 ml) were round in a mortar pestle to a fine paste. Dibromo-olefin **35** (0.568 g, 2 mmol) was dissolved in dry

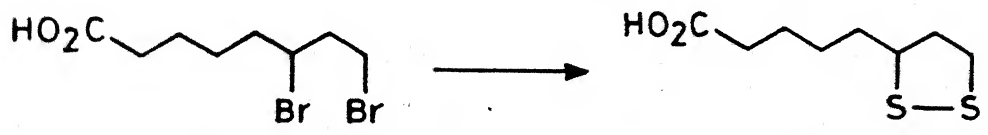
dichloromethane (10 ml) and to it was added with constant stirring $KMnO_4$-$CuSO_4$ mixture in portions. Finally tert-butyl alcohol (1 ml) was added and the reaction mixture was stirred for 2 h. The reaction mixture was worked up by filtering over Celite. It was washed with sufficient amount of dichloromethane, dried (anhyd. $MgSO_4$) and concentrated to give the dibromo acid **36** (0.507 g, 84%).

IR ($CHCl_3$) : 3350, 3080, 1700 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.42-1.92 (br,s. 8 H); 2.12-2.34 (m, 2 H); 3.43-3.68 (t, 2 H); 3.93-4.28 (m, 1 H), 10.06 (br,s, 1 H).

MS (m/e) : 274 (M^++4), 272 (M^++2), 270 (M^+).

Reaction of Dibromo acid **36** with Tetrathiotungstate **6**



36 **37**

To a solution of piperidinium tetrathiotungstate **6** (0.484 g, 1 mmol) in dimethyl formamide (10 ml)was added dropwise with constant stirring the dibromo acid **36** (0.302, 1 mmol). The reaction was carried out at 50 °C for 4 h to give lipoic acid **37** (0.132 g , 65%), m.p. 45-47 °C (lit.[16] m.p. 46-48.5 °C).

IR ($CHCl_3$) : 1700 cm^{-1}.

^{1}NMR ($CDCl_3$) : δ 1.60 (br,s, 8 H); 2.13-2.37 (m, 2 H); 3.08 (t, 2 H); 3.50 (m, 1 H); 10.06 (s, 1 H).

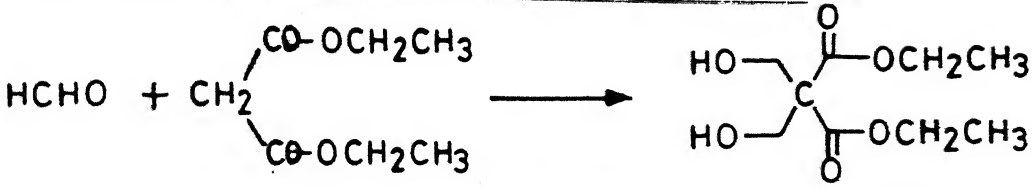
MS (m/e) : 206 (M^+).

Anal. Calcd for $C_8H_{14}O_2S_2$: C, 46.60; H, 6.80.

Found : C, 46.63; H, 6.79.

Asparagusic Acid Synthesis 41

Preparation of Diethyl bis(hydroxymethyl)malonate 39



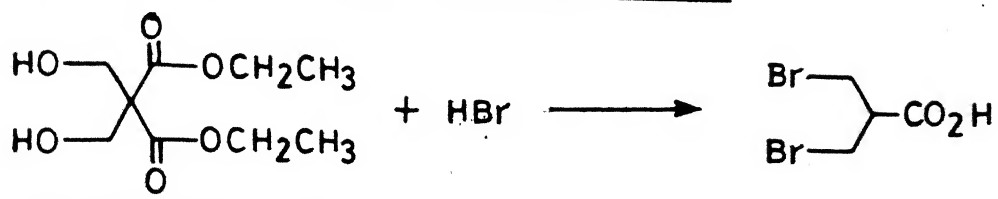
Formaldehyde solution (30%) (24.35 ml, 300 mmol) and K_2CO_3 (0.787 g, 5.7 mmol) were kept below 20 °C to prevent the polymerization of formaldehyde while the mixture was being stirred, diethyl malonate (15.18 ml, 100 mmol) was added at a very slow rate. After the addition was complete, stirring was continued for 1 h. The contents were shaken thoroughly with ammonium sulfate solution and extracted with diethyl ether (4x20 ml) and dried (anhyd. $MgSO_4$). The ether and the excess formaldehyde were removed by distillation and the residual liquid was placed in an ice bath until crystals appeared. Diisopropyl ether (50 ml) was then added and the mixture was warmed to 50 °C until all the crystals dissolved. The solution in the ice bath was stirred until a thick suspension of crystals formed and was left there for an additional 2 h. The white crystals obtained after filtration were dried in vacuum to give diethyl bis(hydroxymethyl)malonate 39 (23.56 g, 74%), m.p. 46-48 °C (lit.[49] 48-50 °C).

IR ($CHCl_3$) : 3430, 1735 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.0-1.33 (t, 6 H); 3.53-3.73 (br,s, 2 H);

4.06 (s, 4 H); 4.0-4.43 (q, 4 H).

Preparation of β,β'-Dibromo-isobutyric acid

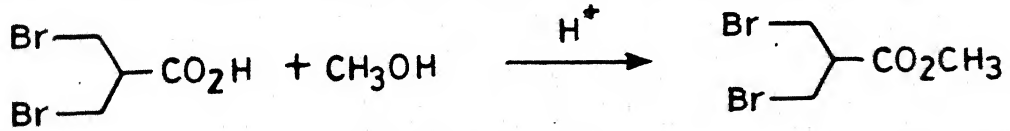


Diethyl bis(hydroxymethyl)malonate (3.16 g, 10 mmol), 48% hydrobromic acid (8 ml) were combined and heated until C_2H_5Br began to distil. After this liquid ceased to boil, the reaction contents were refluxed for 6 h. The product was crystallized out of solution by placing it in an ice bath for 3 h. The solid was filtered, washed with ice water, and dried as before. Second fraction of crystals was obtained by removing approximately 4 ml of liquid from the filtrate to give the dibromo acid (1.501 g, 70%, m.p. 98-100 °C (lit.[49] m.p. 100-102 °C).

IR (KBr) : 3300-3100, 1700 cm^{-1}.

^1H NMR (CCl_4) : δ 3.10-3.28 (m, 1 H); 3.7-3.75 (d, 4 H); 9.2-9.54 (br,s, 1 H).

Preparation of Methyl ester of Dibromo isobutyric acid **42**

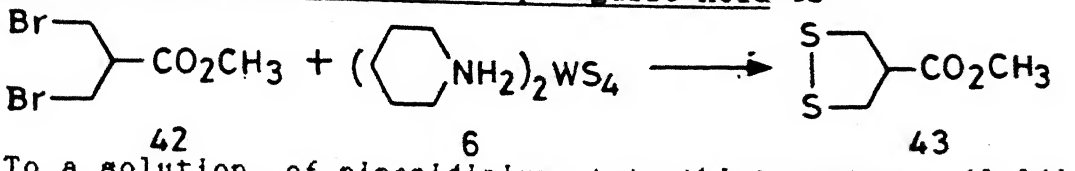


Dibromo isobutyric acid (1 g, 4.67 mmol) in CH_3OH (5 ml) and 1 drop conc. H_2SO_4 was refluxed for 12 h to give compound **42** (1.108 g, 91%), b.p. 70-72 °C (lit.[49] b.p. 72 °C).

IR (thin film) : 1740 cm^{-1}.

^{1}H NMR ($CDCl_3$) : δ 2.96-3.25 (m, 1 H); 3.62-3.65 (d, 4 H); 3.7 (s, 3 H).

Preparation of Methyl Ester of Asparagusic Acid **43**[32]



42 **6** **43**

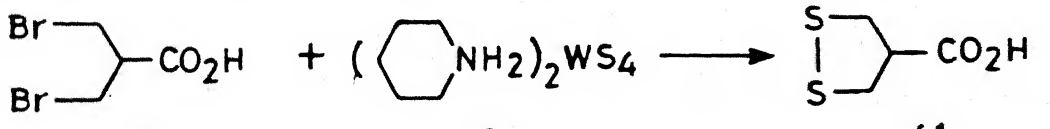
To a solution of piperidinium tetrathiotungstate (0.968 g, 2 mmol) in dimethyl formamide (12 ml) was added dropwise with constant stirring compound **42** (0.520 g, 2 mmol). The reaction was allowed to go for 4 h at ~28°C. It was worked up the same way as described earlier. Chromatographic purification using 25% ether/petroleum ether (40-60°C) as eluent gave the methyl ester of asparagusic acid **43** (0.232, 72%).

IR ($CHCl_3$) : 1740 cm^{-1}.

^{1}H NMR ($CDCl_3$) : δ 2.97-3.06 (m, 1 H); 3.21-3.28 (d, 4 H); 3.68 (s, 3 H).

MS (m/e) : 164 (M^+), 133, 132, 105, 104.

Reaction of Dibromo acid **40** with **6**



40 **6** **41**

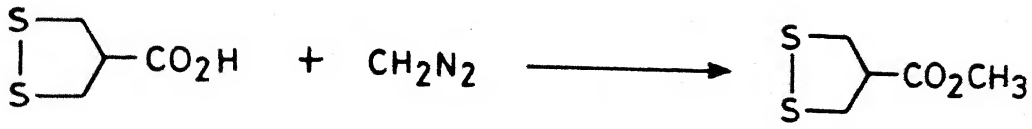
To a stirred solution of piperidinium tetrathiotungstate (0.968 g, 2 mmol) in dimethyl formamide (10 ml) was added a solution of dibromo acid **40** (0.492 g, 2 mmol) in dimethyl formamide (10 ml). The reaction mixture was allowed to stir for 5

h. It was worked up as described earlier to yield the asparagusic acid **41** (0.182 g, 77%), m.p. 74-76 °C (lit.[32] m.p. 75.7-76.5 °C).

IR ($CHCl_3$) : 3500, 1700 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 2.95-3.08 (m, 1 H); 3.22-3.29 (d, 4 H); 10.43 (s, 1 H).

Preparation of the Methyl ester **43** from **41**



Diazomethane generated from `Diazald' (1.2 g) was added in portions to a stirred solution of **41** (0.300 g, 2 mmol) in ether (5 ml) at 0 °C. Progress of the reaction was monitored periodically by TLC for 1-2 h. Excess diazomethane was destroyed by the addition of a few drops of acetic acid. Water (20 ml) was added and the layers separated. The aq. layer was extracted with (2x15 ml) portions of ether. The combined ethereal extracts were successively washed with sat. sodium bicarbonate solution, water, brine and dried over anhydrous magnesium sulfate. The solvent was evaporated to yield product **43** (0.209 g, 64%).

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CHAPTER III

CHEMISTRY OF TETRATHIOTUNGSTATE: A NOVEL SYNTHESIS OF DISULFIDES FROM SULFONYL DERIVATIVES

3.1 INTRODUCTION

Since sulfonyl chlorides are easily prepared by the chlorosulfonation of arenes and alkanes[1] their conversion to other organic sulfur compounds with sulfur in the lower oxidation state is synthetically useful. Among these, organic disulfides are important from the point of view of biological activity,[2] industrial utility[3] and as valuable starting materials for the synthesis of a variety of sulfenyl[4] and sulfinyl[5] compounds. Thus the reductive coupling of sulfonyl chlorides to the corresponding disulfides constitutes an important synthetic methodology.

A wide variety of reagents are known to reduce the sulfonyl halides to the corresponding disulfides. Both arene and alkane sulfonyl chlorides are reduced to disulfides by hexacarbonyl molybdenum in dry tetramethylurea (55-88%).[6] Carbonyl complexes of Ni, Fe or Cr reduce sulfenyl chlorides to disulfides below 0^{o}C in yields above 90%,[7] but the synthetic value of this reaction is dubious for most situations since sulfenyl chlorides not only are commonly made from disulfides

but are readily and quantitatively reduced to disulfides simply by iodide ion[8] (Eqn. 3.1):

$$2\ RSCl + 2\ KI \longrightarrow RSSR + I_2 + 2\ KCl \qquad .. (3.1)$$

An arene sulfonyl chloride (but not an ester) is also reduced by trichlorosilane in benzene with amine catalysis, as are sulfinyl and sulfenyl chlorides or their esters (53-91%) and the mechanisms of the reaction are still unclear.[9]

Phosphite esters reduce arene sulfonyl chlorides, arene sulfenyl chlorides (ArSCl) or thiolsulfonates ($ArSO_2SAr$) to disulfides, along with other products.[10] Triaryl phosphines (R_3P) reduce arene sulfonyl chlorides to thiols and sulfinic acids, as well as to disulfides, and also reduce α-disulfones (RSO_2SO_2R), thiolsulfonates (RSO_2SR) or polysulfides (RS_xR) to disulfides.[10] Care is necessary because phosphites and phosphines can desulfurize disulfides to monosulfides.

An intriguing and promising reaction has been used to make unsymmetrical disulfides in 47-82% yield. In this, sulfenates are reduced as shown[11] (Eqn. 3.2):

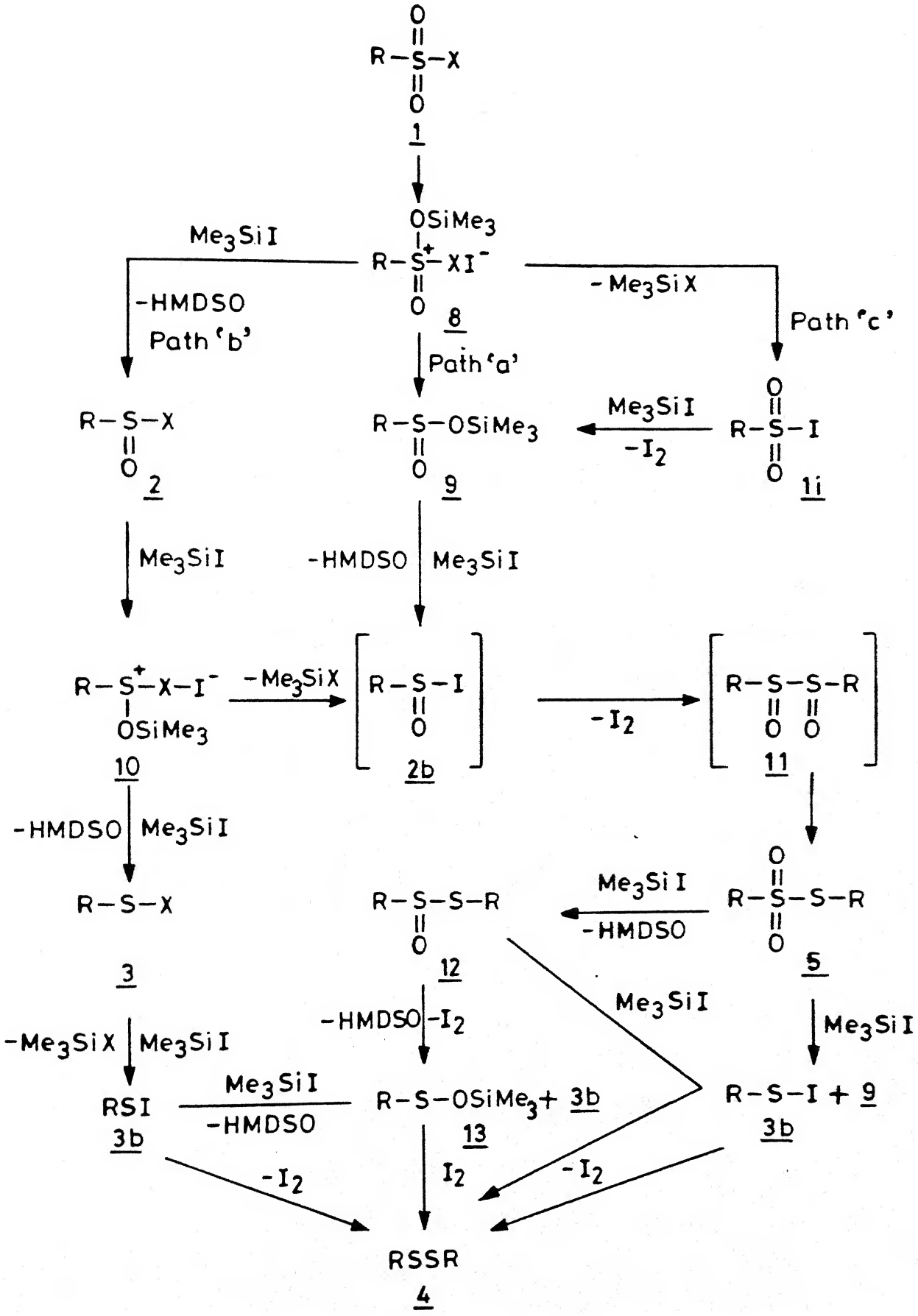
$$3\ PhSOMe + (RS)_3B \longrightarrow 3\ PhSSR + (MeO)_3B \qquad .. (3.2)$$

Diphosphorus tetraiodide,[12] aluminium iodide[13] and chlorotrimethylsilane/sodium iodide reagent system[14] are also known to convert the sulfonyl chlorides to the corresponding disulfides.

Thiolsulfonates were found to be the intermediates in the conversion of sulfonyl and sufinyl chlorides to the corresponding disulfides using chlorotrimethylsilane/sodium iodide system and a possible mechanism has been proposed[14b] (**Scheme 3.1**). The reaction of sulfonyl halides **1** with iodotrimethylsilane is most likely initiated by the formation of the sulfoxonium salt **8**, which can further react in three different ways. The attack of the iodide anion on the halogen atom in **8** (path `a') may lead to silyl sulfinate **9** which, in turn, on treatment with iodotrimethylsilane splits off hexamethyldisiloxane (HMDSO) and give sulfinyl iodide **2b**. Compound **2b** couples to α-disulfoxide **11**, which rearranges to the stable and isolable thiolsulfonate **5**. Its further reduction to disulfide by iodotrimethylsilane occurs *via* thiolsulfinate **12** and/or sulfenyl iodide **3b** as shown in **Scheme 3.1**. The salt **8** can also react with second molecule of iodotrimethylsilane (path `b') to give sulfinyl halide **2**, which may be transformed into **3** *via* **10** or converted into **3b** upon reacting with iodotrimethylsilane. Finally, the attack of iodide anion on the positively charged sulfur atom in **8** followed by elimination of chlorotrimethylsilane (path `c') may result in the formation of sulfonyl iodide undergoing the reduction according to path `a'. Mechanistic details of the conversion of sulfonyl halides to the corresponding thiolsulfonates was worked out by Palumbo.[15]

In 1969, Alper[6] found that the reaction of sulfonyl chlorides with the hexacarbonyl molybdenum in anhydrous tetramethyl urea provides a facile method for obtaining a variety of

Scheme - 3.1


R–S(=O)(=O)–X
1
OSiMe3
R–S+(=O)(=O)–XI−
8
Me3SiI
-HMDSO
Path 'b'
Path 'a'
-Me3SiX
Path 'c'
R–S(=O)(=O)–X
2
R–S(=O)(=O)–OSiMe3
9
Me3SiI
-I2
R–S(=O)(=O)–I
1i
Me3SiI
-HMDSO
Me3SiI
R–S+(–X–I−)(–OSiMe3)
10
-Me3SiX
R–S(=O)(=O)–I
2b
-I2
R–S(=O)(=O)–S(=O)(=O)–R
11
-HMDSO
Me3SiI
R–S–X
3
R–S(=O)(=O)–S–R
12
Me3SiI
-HMDSO
R–S(=O)(=O)–S–R
5
-Me3SiX
Me3SiI
-HMDSO
-I2
Me3SiI
RSI
3b
Me3SiI
-HMDSO
R–S–OSiMe3 + 3b
13
R–S–I + 9
3b
-I2
I2
-I2
RSSR
4

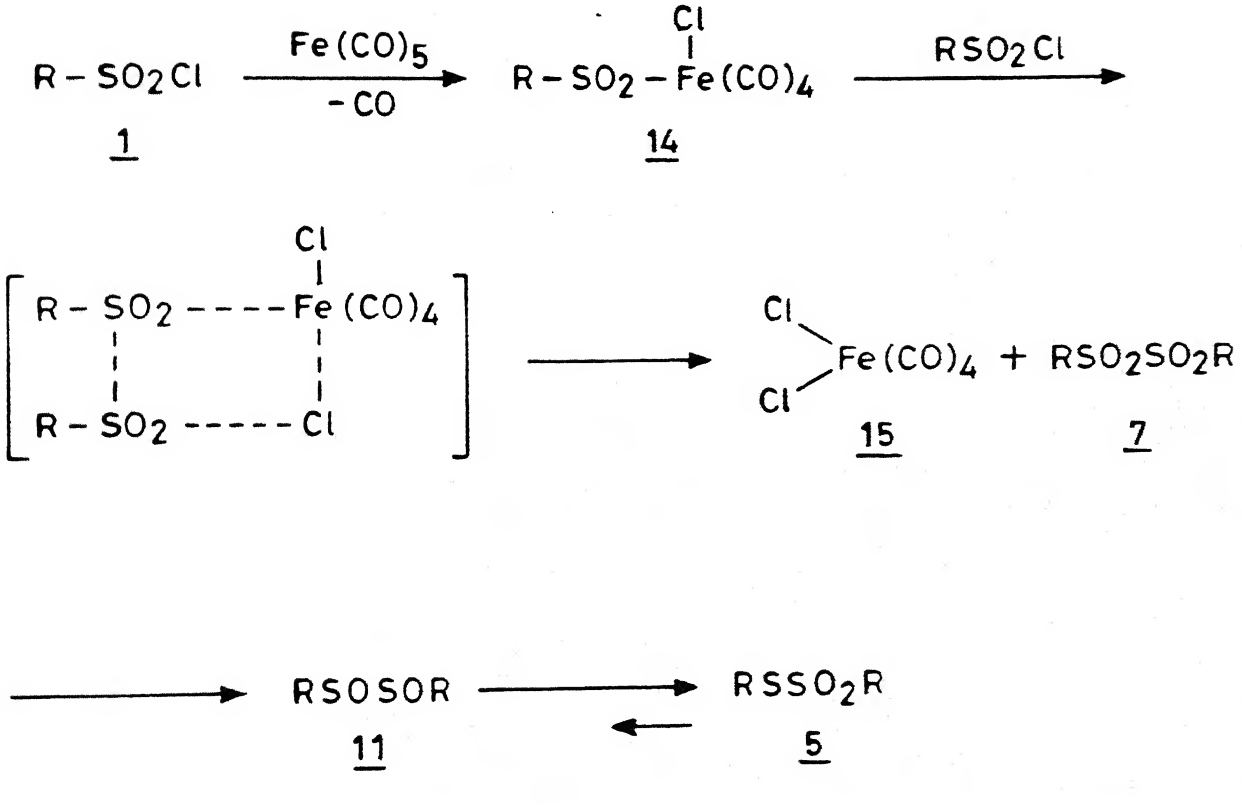
disulfides (Eqn. 3.3):

$$\underset{1}{RSO_2Cl} \xrightarrow[\text{in TMU}]{Mo(CO)_6} \underset{4}{RSSR} \qquad .. (3.3)$$

Here, the metal carbonyl does not function as a catalyst. This is the first report in the literature wherein an inorganic complex has been used to effect this transformation. The yields in this reaction varied from 55-75%. Hexacarbonyl-chromium and tungsten proved to be relatively ineffective reagents for this transformation. The above reaction was carried out at 70 ^{o}C with stirring under nitrogen atmosphere for 2.0-2.5 h and heated to 100 ^{o}C for 10-15 minutes. When sulfonyl chlorides were treated with $Fe(CO)_5$,[16] thiolsulfonates were obtained instead of disulfides in 36-71% yield. A postulated mechanism for the reaction of sulfonyl halide with ironpentacarbonyl is given in **Scheme 3.2**. It involves initial formation of a sulfur-iron σ complex **14**. Complex **14** can then react with additional sulfonyl chloride to give rise to disulfone **7** and the fairly unstable halogenometal carbonyl **15** possibly *via* a four center transition state. Deoxygenation of **7** with iron carbonyl produces the disulfoxide **11** which is known to exist as the thiolsulfonate tautomer **5**. The reaction of sulfonyl halide with hexacarbonyl molybdenum is believed to go *via* the intermediacy of thiolsulfonates **5** (**Scheme 3.3**).

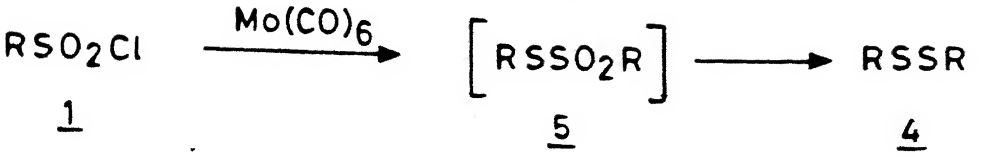
Harpp[17] reported recently an interesting observation where a persulfido complex $Mo_2S_{12}^{2-}$ induces the formation of *p*-tolyl disulfide from *p*-toluene sulfonyl chloride in acetonitrile at

Scheme - 3.2



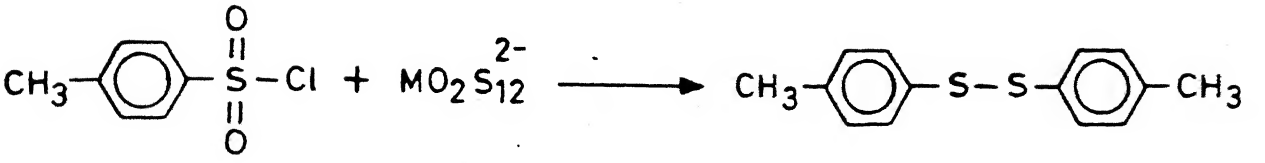
1 14 15 7 11 5

Scheme - 3.3



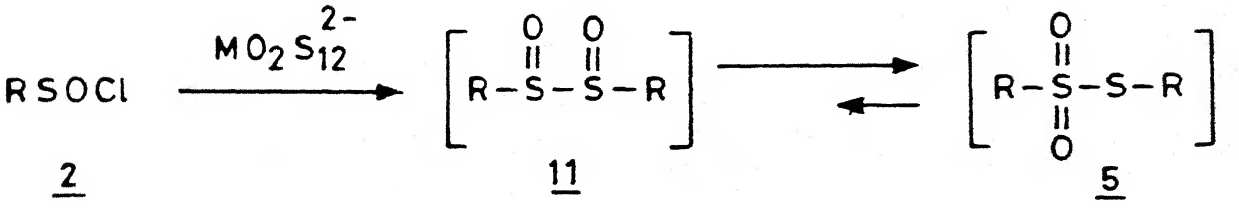
1 5 4

Scheme - 3.4

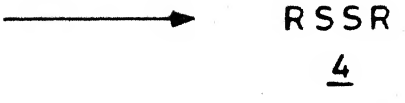


1b 4b

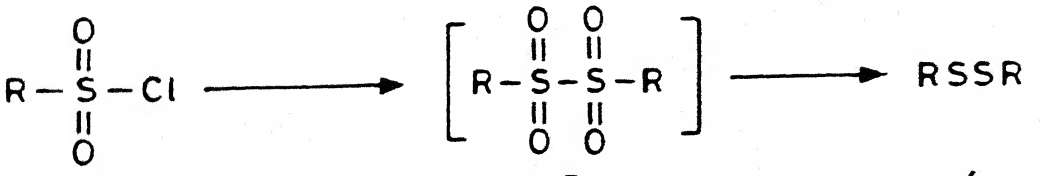
Scheme - 3.5



2 11 5

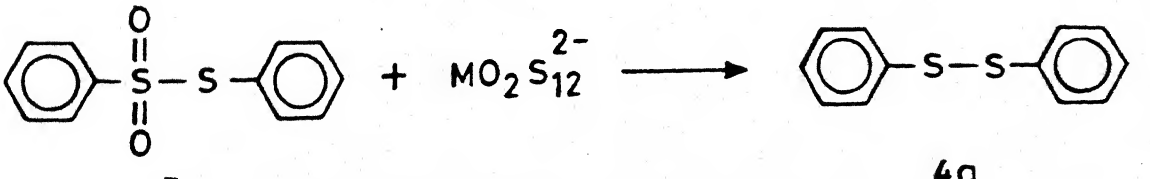


4



1 7 4

Scheme - 3.6



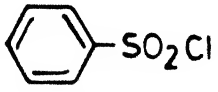
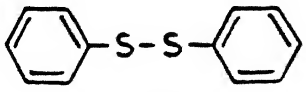
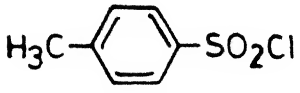
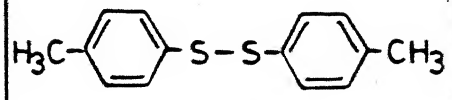
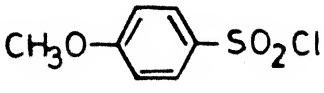
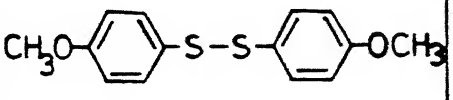
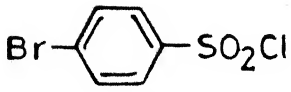
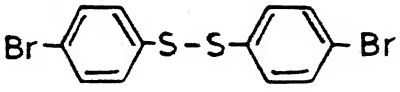
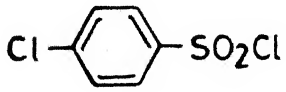
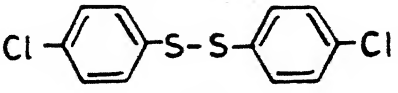
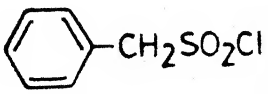
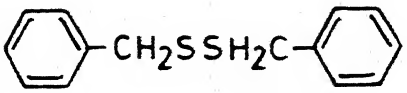
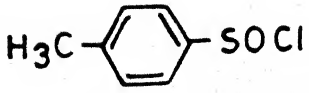
5a 4a

80 °C in 8 h. This is the first example where a thiometallate has been used for this type of transformation (Scheme 3.4). Although no intermediates have been isolated, Harpp and MacDonald[17] feel that the reaction pathway involves the formation of, in the sulfinyl case, an α-disulfoxide 11 (which would be expected to rearrange to the thiolsulfonate[18]) or in the sulfonyl chloride system, the α-disulfone 7 (Scheme 3.5). Support for this pathway was obtained when a sample of benzenethiolsulfonate was refluxed in acetonitrile with complex $Mo_2S_{12}^{2-}$ for 4 h under a nitrogen atmosphere to yield 81% of the phenyl disulfide (Scheme 3.6).

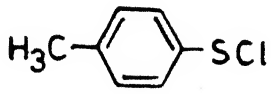
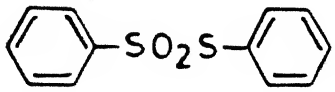
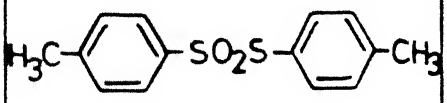
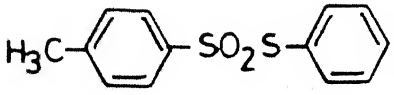
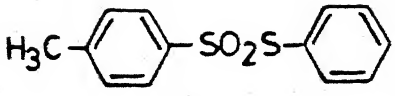
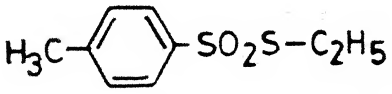
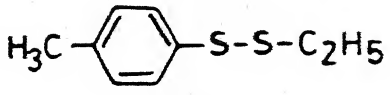
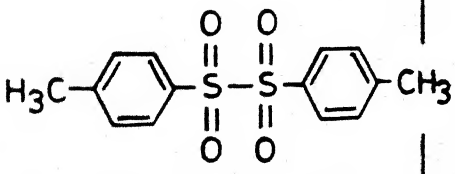
In the light of our success towards the synthesis of disulfides from alkyl halides using tetrathiometallates (M = Mo, W) in both inter and intramolecular reactions, we decided to explore the reactivity of tetrathiotungstates with sulfonyl derivatives and study the scope and limitation of such a reaction.

3.2 RESULTS AND DISCUSSION

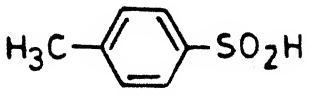
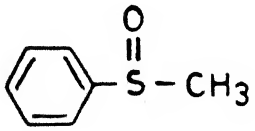
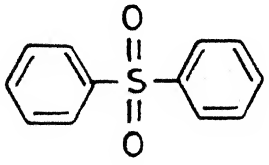
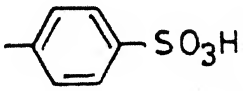
Earlier we have shown that alkyl halides can be converted to the corresponding disulfides in excellent yields using piperidinium tetrathiometallates, ( NH_2)MS_4 (Chapter 1 and 2). While exploring further the synthetic utility of tetrathiotungstate 6, we observed a novel transformation in the reaction of sulfonyl derivatives to the corresponding disulfides (Eqn. 3.4):

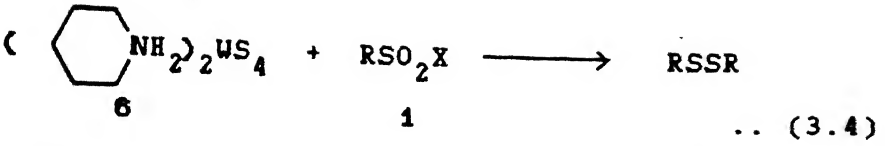
Entry	Substrate	Time (h)	Product	Yield (%)
1	 1a	2.0	 4a	78
2	 1b	2.0	 4b	69
3	 1c	2.5	 4c	61
4	 1d	2.0	 4d	53
5	 1e	2.0	 4e	57
6	 1f	4.0	 4f	59
7	$CH_3CH_2CH_2CH_2SO_2Cl$ 1g	3.0	$CH_3(CH_2)_2CH_2-S\rightarrow_2$ 4g	41
8	CH_3SO_2Cl 1h	3.0	CH_3SSCH_3 1h	100
9	 2	0.5	4b	96

Contd ----

Entry	Substrate	Time (h)	Product	Yield (%)
10	 3	0.5	4b	88
11	 5a	0.5	4a	67
12	 5b	0.5	4b	92
13	 5c	0.5	4a  21a 4b	
14	 5d	1.0	4b  21b $C_2H_5SSC_2H_5$ 21c	
15	 7	12	4b	88

Contd ----

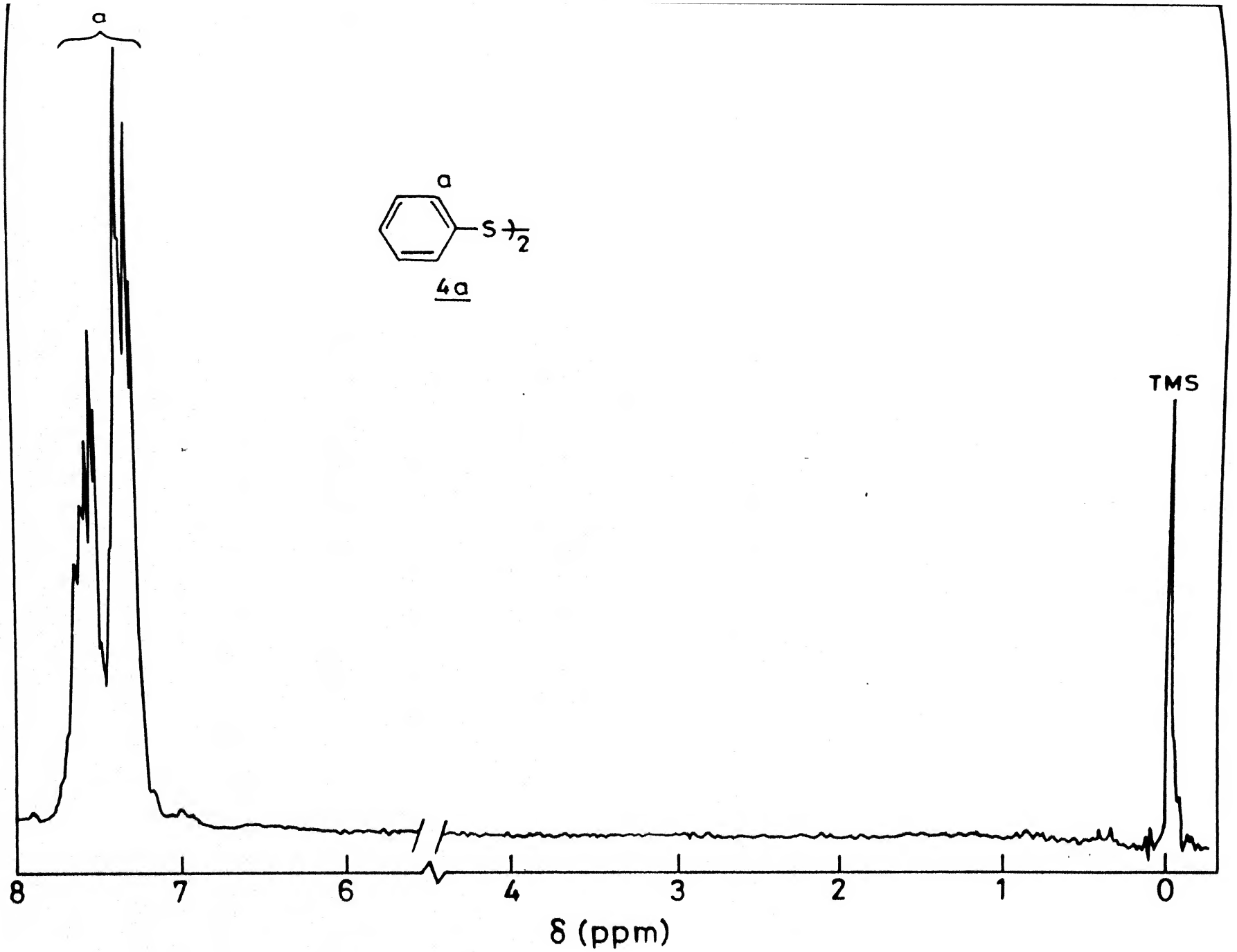
Entry	Substrate	Time (h)	Product	Yield (%)
16	 16	0.5	4b	98
17	 17	24	NO REACTION	
18	 18	24	NO REACTION	
19	 19	24	NO REACTION	



6 1 .. (3.4)

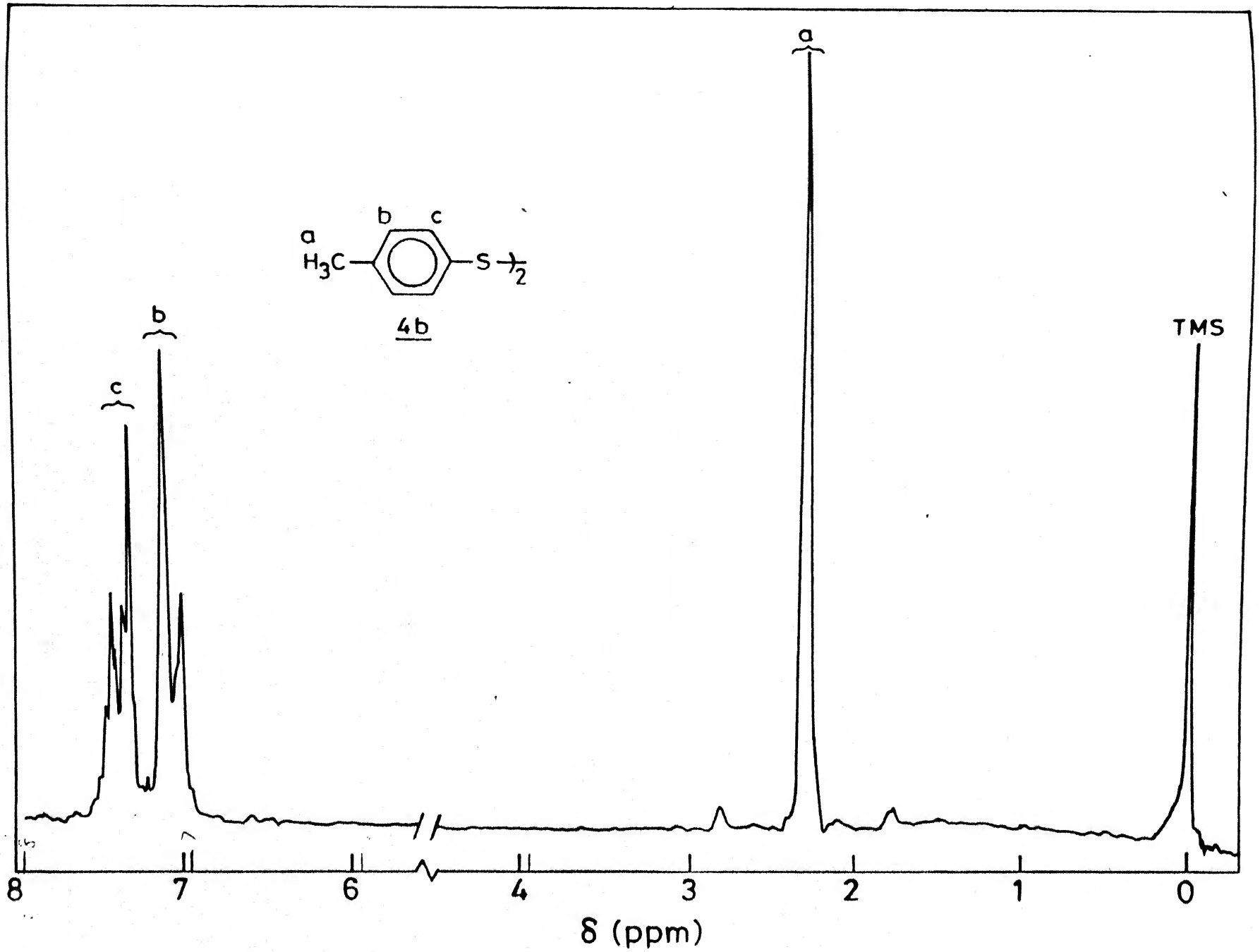
Aryl and alkyl sulfonyl chlorides react rapidly with a mole equivalent of **6** at room temperature to afford the corresponding disulfides in good yields (entries 1-8, **Table 3.1**). Thus, benzene sulfonyl chloride **1a** reacted with **6** to give phenyldisulfide **4a** in 78% yield (DMF, 2 h). Similarly, toluene sulfonyl chloride **1b**, p-bromobenzene sulfonyl chloride **1d** and p-chlorobenzene sulfonyl chloride **1e** reacted with **6** to give the corresponding disulfides **4b**, **4d** and **4e** (DMF, 2 h) in 69, 53 and 57% yield, respectively. The reaction of p-methoxybenzene sulfonyl chloride **1c** took 2.5 h to go to completion to give the corresponding p-methoxyphenyldisulfide **4c** in 61% yield. α-Toluene sulfonyl chloride **1f** took a longer time (4 h) to react with **6** to give disulfide **4f** in 59% yield. Butane sulfonyl chloride **1g** and methane sulfonyl chloride **1h** gave the corresponding disulfides (DMF, 3 h) **4g** and **4h** in 41 and 100% yield, respectively. As can be seen from the **Table 3.1**, in terms of reactivity, alkyl sulfonyl chlorides react with **6** slower than the aryl sulfonyl chlorides.

p-Toluenesulfinyl chloride **2** (entry 9) and p-toluenesulfenyl chloride **3** (entry 10) were also smoothly converted to disulfide **4b** (DMF, 0.5 h) in 96 and 88% yield, respectively. p-Toluenesulfinic acid **16** (entry 16) was also converted to the corresponding disulfide **4b** (DMF, 0.5 h) in almost quantitative yield. However, it is interesting to note that sulfoxide **17** (entry 17), sulfone **18** (entry 18) and sulfonic acid **19** (entry



4a

^{1}H NMR spectrum (80 MHz) of 4a



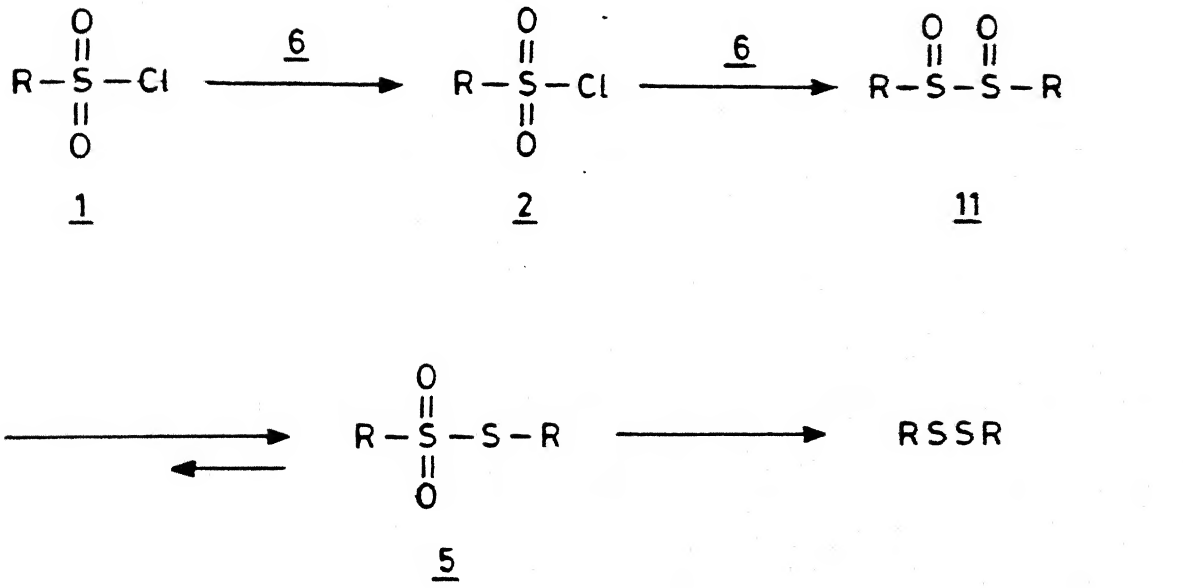
^{1}H NMR spectrum (80 MHz) of 4b

19), remained unaffected on treatment with **6** even after long reaction time (DMF, 24 h).

Although no intermediates have so far been isolated in these reactions, a preliminary investigation has revealed some interesting facts. Reductive dimerization of sulfonyl chloride **1** and sulfinyl chlorides **2** to disulfides are generally believed to go through different stages[17] as shown in Scheme 3.7

In order to test the validity of the intervention of these intermediates in our reaction, authentic samples of α-disulfone **7**[19] and thiosulfonate esters **5a-d** were prepared and subjected to reaction with **6**. Although ptolyltoluene benzenethiolsulfonate **5b**[20] and phenylbenzenethiolsulfonate **5a**[21] gave the corresponding disulfides **4b** and **4a** in 92 and 67% yields, respectively in less than 0.5 h, the disulfone **7** took nearly 12 h to react with **6** to give the corresponding disulfide **4b** (88%). Hence it is very unlikely that the α-disulfones **7** are the intermediates in the overall transformation. The fact that thiolsulfonate esters **5a-d** react almost instantaneously to give the products suggest that they are more likely to be the intermediates in the reaction although they could not be detected or isolated as intermediates in the reaction. The reaction of sulfonyl chloride **1** with tetrathiotungstate **6** was performed at a lower temperature (-20 ^{o}C) and the order of addition reversed such that at no instant, excess of the reagent was present in the reaction medium. Monitoring the reaction by TLC showed only the unreacted starting material and the product, implying that

Scheme-3.7



the subsequent steps are much faster than the initial reaction. Since sulfinyl chloride 2 reacts faster than sulfonyl chloride, we believe the overall transformation probably goes as indicated in Scheme 3.7 where compound 1 gets converted to the sulfinyl chloride 2, which then undergoes oxidative coupling to give α-disulfoxide 11. These α-disulfoxides 11 are known[21] to rearrange readily to the thiolsulfonate esters 5, which further undergo reduction to give the disulfides.

In the case of reduction of thiolsulfonates by 6, one would anticipate the formation of unsymmetrical disulfides starting from thiolsulfonate esters having different substituents at the sulfonyl and sulfenyl sulfur. However, in the reaction of 5c[22] and 5d[23] with 6, a mixture of unsymmetrical and both possible symmetric disulfides was always produced in a ratio of 2:1:1. This could be due to the disproportionation of the unsymmetrical disulfide formed upon reduction or rather by cleavage of the S-S bond in thiolsulfonate[14b] by 6 initially and reformation of the bond later.

Attempts to crystallize out the inorganic material from the reaction mixture proved futile. Nevertheless, it would still be of interest to study how tetrathiotungstates 6 brings about this interesting transformation.

At the present time, however, it could be used as a mild and efficient methodology for the synthesis of disulfides from sulfonyl derivatives.

3.3 EXPERIMENTAL

Experimental Procedure

All the reactions were performed in oven dried apparatus. Reaction mixture were stirred magnetically unless otherwise specified. Reaction product solutions were concentrated using a Perfit rotary evaporator and products were characterized by comparison with authentic samples (spectra, T.L.C.,m.p.). Lassaigne's test was performed on each compound for detection of sulfur.

Materials

Commercial grade solvents were distilled prior to use. Dimethyl formamide was initially purified by azeotropic distillation with benzene. The residual solvent was shaken with calcium oxide, filtered and distilled at reduced pressure. The fraction having b.p. 76 ^{o}C/39 mm Hg was collected. The distillate was stored over type 4 Å molecular sieves.

Chromatography

Analytical thin layer chromatography was performed on Merck precoated glass backed silica gel 60F-254 0.25 mm plates. Visualization of the spots was effected by one or more of the following techniques: (a) ultraviolet illumination; (b) exposure to iodine vapour; (c) immersion of the plate in a 10% solution of phosphomolybdic acid in ethanol followed by heating to ca. 200 ^{o}C.

Column chromatography was performed using 60-120 and 100-

200 mesh Acme silica gel. The flash chromatography was performed using Merck thin-layer chromatography silica gel.

Physical Data

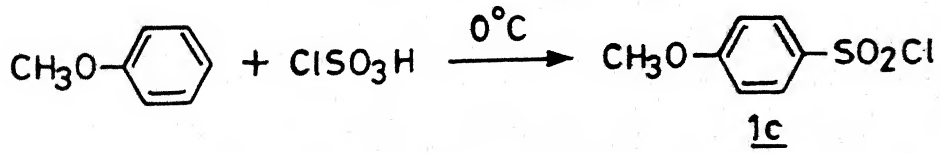
Melting points (m.p.) were determined with a uni-melt capillary melting point apparatus and are uncorrected. Boiling points (b.p.) are uncorrected.

Bulb to bulb distillation was carried out on a Büchi-GKR-50 distillation unit.

Infrared (IR) spectra were recorded on Perkin-Elmer model 1320 and 580 spectrophotometers and are reported in wave numbers (cm^{-1}).

Proton magnetic resonance (PMR) spectra were recorded at 90 MHz on a Varian EM-390 instrument, at 80 MHz on Bruker WP-80 instrument and at 90 MHz on Jeol FX-90Q instrument. Chemical shifts are reported in parts per million down field from internal reference tetramethyl silane (TMS) (δ). Multiplicity is indicated using the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad); etc. Mass spectra (MS) were recorded on a Jeol TMS D-300 mass spectrometer. Principal molecular fragments are reported.

Preparation of p-Methoxybenzenesulfonyl chloride 1c



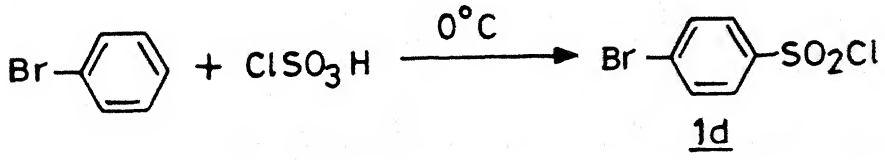
1c

Chlorosulfonic acid (19.5 ml, 0.293 mol) was placed in a flask and cooled to 0 °C. Anisole (10.8 g, 0.1 mol) was added dropwise with stirring at such a rate that temperature of the mixture did not rise above 5 °C. After the addition of anisole, the reaction mixture was stirred for 4 h and allowed to stand overnight in freezing mixture. The liquid was poured on crushed ice and the aqueous solution separated from the oily layer and the latter washed several times by decantation with cold water. The oil was cooled at -10 ° to -20 °C for several hours. The almost pure p-methoxybenzenesulfonyl chloride 1c crystallizes out from petroleum ether (40-60 °C) (12.20 g, 59%), m.p. 41 °C (lit.[24] m.p. 42 °C).

IR ($CHCl_3$) : 1390, 1180 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 3.92 (s, 3 H); 6.73-6.81 (d, 2 H); 7.66-7.75 (d, 2 H).

Preparation of p-Bromobenzenesulfonyl chloride 1d



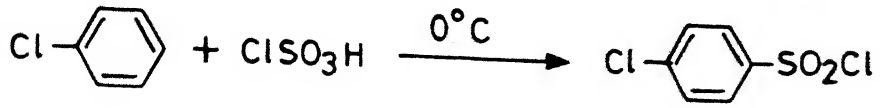
1d

This was prepared by the above procedure using bromobenzene (10.5 ml, 0.1 mole) and chlorosulfonic acid (19.5 ml, 0.29 mole). p-Bromobenzenesulfonyl chloride 1d was obtained as a solid (12.53 g, 49%), m.p. 75 °C (lit.[25] m.p. 76 °C).

IR (KBr) : 1385, 1195 cm^{-1}.

^1H NMR (CCl_4) : δ 7.77 (d, 2 H); 7.93 (d, 2 H).

Preparation of p-Chlorobenzenesulfonyl chloride **1e**



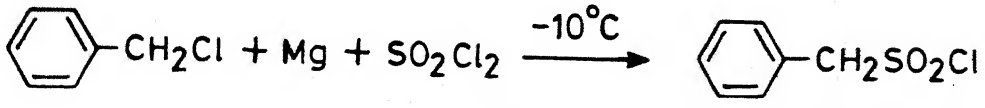
1e

This was prepared by above procedure using chlorobenzene (10.2 ml, 0.1 mol) and chlorosulfonic acid (19.5 ml, 0.29 mol). p-Chlorobenzenesulfonyl chloride **1e** was obtained as a solid (10.77 g, 51%), m.p. 49-50 °C (lit.[25] 50-52 °C).

IR (KBr) : 1388, 1195 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 7.53-7.75 (d, 2 H); 7.93-8.12 (d, 2 H).

preparation of α-Toluenesulfonyl chloride **1f**



1f

Magnesium powder (1.22 g, 50 mmol) was taken in dry ether (5 ml) in a three necked flask fitted with a reflux condenser and a dropping funnel and to it was added dropwise a solution of benzyl chloride (5.75 ml, 50 mmol) in dry ether (25 ml). After the formation of Grignard, the reaction flask was cooled to -10 °C and sulfuryl chloride (3.09 ml, 50 mmol) was added dropwise during 10 minute period. The reaction mixture was allowed to stir for 1 h. The reaction was brought to room temperature and was filtered through celite pad and washed with benzene. The organic layer was concentrated to give α-toluenesulfonyl chloride **1f** (6.01 g, 63%), m.p. 92°C (lit.[26] m.p. 94 °C).

IR (KBr) : 3020, 2970, 2862, 1600, 1185 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 4.84 (s, 2 H); 7.43-7.56 (s, 5 H).

Preparation of Butanesulfonyl chloride **1g**

$$BuLi + SO_2Cl_2 \xrightarrow{-50^\circ C} BuSO_2Cl$$

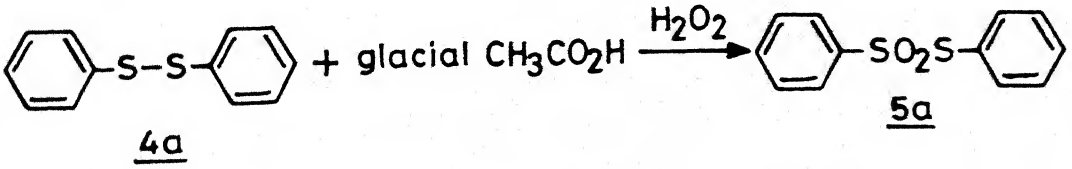
1g

To a solution of sulfuryl chloride (13.19 g, 60 mmol) in dry hexane (10 ml) under nitrogen atmosphere was added dropwise at -50 °C with stirring, a solution of 1.78 N (28 ml, 50 mmol) of n-BuLi in hexane. After the addition was complete, the bath temperature was increased to -20 °C and ice-cold water (100 ml) was added. The organic phase was washed with $NaHCO_3$ at 0 °C until there was no CO_2 evolution. It was washed with ice-water (100 ml) and dried (anhydrous $CaCl_2$). Concentration of the organic layer gave the product **1g** (4.82 g, 62%), b.p. 75 °C/10 mm (lit.[27] b.p. 84 °C/13 mm).

IR (thin film) : 1375, 1165 cm^{-1}.

^1H NMR (CCl_4) : δ 0.96-1.12 (t, 3 H); 1.3-2.16 (m, 4 H); 3.4-3.7 (t, 2 H).

Preparation of Phenylbenzenethiolsulfonate **5a**



4a **5a**

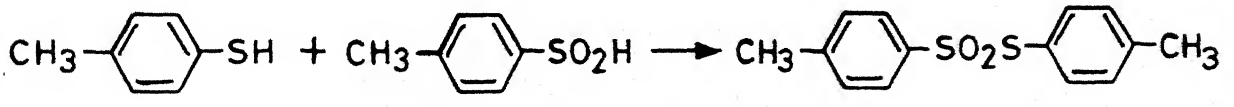
To a suspension of commercially available phenyldisulfide (5.45 g, 25 mmol) in glacial acetic acid (200 ml) was

added dropwise 30% aqueous hydrogen peroxide (5.7 g, 51 mmol) over a period of 0.5 h. After stirring for 24 h at room temperature, cooling precipitated 0.4-0.5 g of product. Dilution of the mother liquor with water (100 ml) caused an oil to separate which was decanted off. The oil and crystals were combined and dissolved in chloroform (100 ml). After washing with aq. saturated $NaHCO_3$ and drying (anhydrous Na_2SO_4), evaporation left 6.04 g of an oil. Chromatographic purification using 1:1 hexane-benzene as eluent gave phenylbenzene thiolsulfonate **5a** (3.46 g, 72%). Recrystallization using CH_3OH gave 3.05 g of colorless crystals, m.p. 36-37 °C (lit.[22] m.p. 36-37 °C).

IR ($CHCl_3$) : 1310, 1133 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 7.31-7.68 (m, 10 H).

Preparation of p-Tolyl-toluenethiolsulfonate **5b**



5b

A solution of thiocresol (1.24 g, 0.010 mol) in benzene (50 ml) was added dropwise to a stirred carbon tetrachloride solution (25 ml) containing Br_2 (1.9 g, 0.012 mol) during 10 minutes at -10 °C. Nitrogen was bubbled through the solution for 40 minutes, to remove the HBr that was formed. Benzene and a mixture of p-toluenesulfinic acid (2 g, 12.82 mol) in H_2O (60 ml) were added to the solution and the stirring was continued for 5 minutes. The reaction mixture was transferred to a

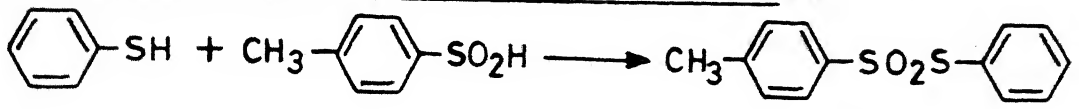
separatory funnel and shaken for 15 minutes. The aqueous phase was removed, and the benzene layer was washed with dilute $NaHCO_3$ solution and H_2O and dried (anhyd. $MgSO_4$). Removal of the solvent *in vacuo* afforded the p-tolyl-p-toluenethiolsulfonate **5b** (1.80 g, 65%), m.p. 73-75 °C (lit.[20] m.p. 76 °C).

IR (KBr) : 1325, 1138 cm^{-1}.

^1H NMR (CCl_4) : δ 2.3 (s, 3 H); 2.4 (s, 3 H); 7.2 (m, 8 H).

MS (m/e) : 278 (M^+), 214, 155, 139, 123, 91.

Preparation of Phenyl-p-Toluenethiolsulfonate **5c**



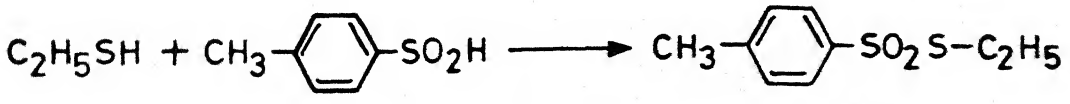
5c

This was prepared by the same procedure as above using thiophenol (1.10 g, 0.01 mol) and p-toluenesulfinic acid (2.0 g, 12.82 mmol). Work-up and removal of the solvent gave phenyl-p-toluenethiolsulfonate (1.79 g, 68%), m.p. 74-76°C (lit.[22,28] m.p. 78 °C).

IR (KBr) : 1325, 1138 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 2.4 (s, 3 H); 6.96-7.43 (m, 9 H).

Preparation of Ethyl-p-toluenethiolsulfonate **5d**



5d

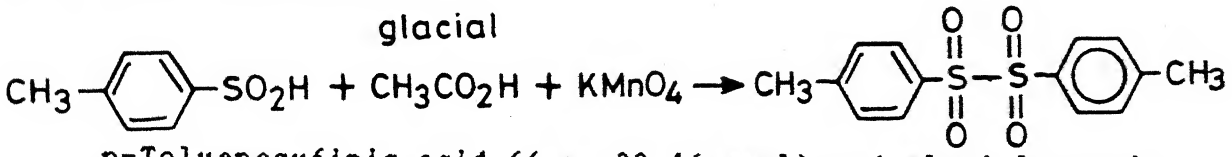
This was prepared by the same procedure as above using ethane thiol (0.62 g, 0.01 mol) and p-toluenesulfinic acid (2.0 g, 12.82 mmol). Work-up and removal of the solvent afforded

the crude ethyl p-toluenethiolsulfonate.[23] Chromatographic purification using 30% dichloromethane-petroleum ether (60-80°C) as eluent afforded pure ethyl-p-toluenethiol-sulfonate[23] (1.34 g, 62%).

IR(thin film) : 2962, 2920, 2865, 1148 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.4 (t, 3 H); 2.4 (s, 3 H); 3.2 (q, 2 H); 7.2-7.8 (m, 4 H).

Preparation of Disulfone 7



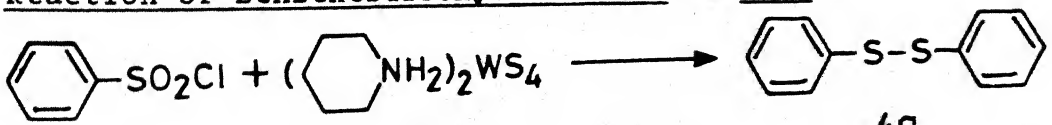
p-Toluenesufinic acid (6 g, 38.46 mmol) and glacial acetic acid (25 ml) were taken in a flask and the reaction mixture was cooled to 0 °C. To this was added 1 g of finely powdered potassium permanganate with stirring. After 5 h the reaction mixture was diluted with water (25 ml) and extracted several times with ether (4x25 ml). The ether extracts were washed with water and dried (anhydrous $MgSO_4$). Organic extracts were evaporated to give 7 as a white solid (1.896 g, 16%), m.p. 208-210 °C (lit.[19] m.p. 212 °C).

IR (KBr) : 1335, 1135 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 2.47 (s, 6 H); 7.45 (m, 4 H); 7.65 (m, 4 H).

MS (m/e) : 310 (M^+), 262,246, 155, 139, 91.

Reaction of Benzenesulfonyl chloride 1a with 6



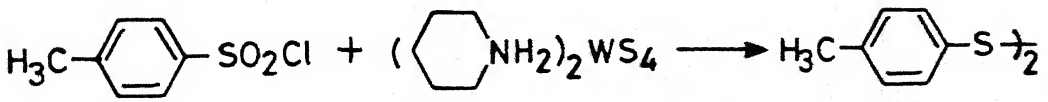
1a 6 4a

To a stirred solution of piperidinium tetrathiotungstate **6** (1.936 g, 4 mmol) in dimethyl formamide (10 ml) was added dropwise benzenesulfonyl chloride **1a** (0.706 g, 4 mmol) in dimethyl formamide (4 ml) at room temperature. The reaction was allowed to go for 2 h. DMF was distilled off under vacuum. The residue was dissolved in dichloromethane (30 ml) and washed several times with water till the aqueous washings were almost colorless. The organic layer was then dried over anhydrous $MgSO_4$ and solvent was removed under reduced pressure to give phenyldisulfide **4a** which on chromatographic purification using 4:1 hexane-benzene as eluent gave pure phenyldisulfide **4a** (0.339 g, 78%), m.p. 58-59 °C (lit.[29] m.p. 60 °C).

IR (KBr) : 3020, 1590, 1500, 750, 700 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 7.21-7.65 (m, 10 H).

Reaction of p-Toluenesulfonyl chloride **1b** with **6**



1b **6** **4b**

To a stirred solution of piperidinium tetrathiotungstate **6** (1.936 g, 4 mmol) in dimethyl formamide (10 ml) was added dropwise p-toluenesulfonyl chloride **1b** (0.764 g, 4 mmol) in dimethyl formamide (4 ml). After 2 h the reaction mixture was worked up as described earlier. Chromatographic purification using petroleum ether (60-80 °C) as eluent gave p-tolyldisulfide **4b** (0.340 g, 69%), mp. 44 °C (lit.[29] m.p. 46 °C).

IR ($CHCl_3$) : 3020, 2960, 2920, 2840, 1570, 1460 cm^{-1}.

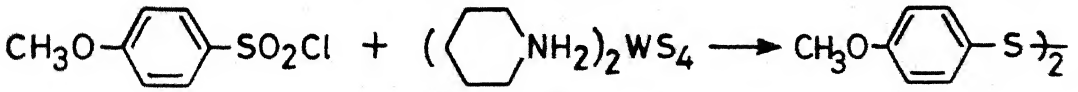
^1H NMR ($CDCl_3$) : δ 2.28 (s, 6 H); 7.0-7.21 (d, 4 H); 7.31-7.5 (d, 4 H).

MS (m/e) : 246 (M^+), 214, 155, 123, 91.

Reaction of p-Toluene sulfonyl chloride **1b** with **6** under controlled conditions

To a stirred solution of p-toluenesulfonyl chloride **1b** (0.190 g, 1 mmol) in dimethyl formamide (2 ml) was added dropwise a solution of piperidinium tetrathiotungstate **6** (0.484 g, 1 mmol) in dimethyl formamide (5 ml) at -20 °C. Monitoring the reaction by TLC showed only the unreacted starting material and the p-tolyl disulfide **4b**.

Reaction of p-Methoxybenzenesulfonyl chloride **1c** with **6**



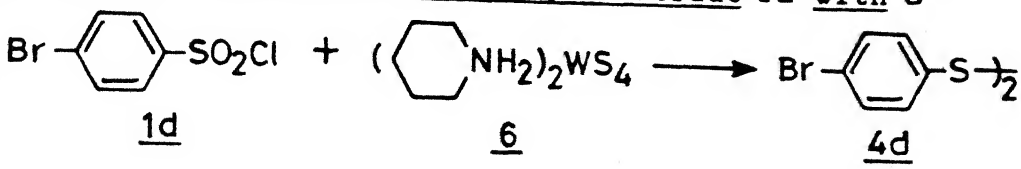
1c **6** **4e**

To a stirred solution of piperidinium tetrathiotungstate **6** (1.936 g, 4 mmol) in dimethyl formamide (10 ml) was added dropwise p-methoxybenzenesulfonyl chloride **1c** (0.827 g, 4 mmol) in dimethyl formamide (4 ml). The reaction took 2.5 h to go to completion. It was worked up the same way as described earlier. Chromatographic purification using 25% dichloromethane-petroleum ether (60-80 °C) as eluent gave bis-(p-methoxyphenyl)disulfide **4c** (0.340 g, 61%), m.p. 70-72 °C (lit.[29] m.p. 73.5°C).

IR (KBr) : 3020, 1245, 1065, 815 cm^{-1}.

^1H NMR (CCl_4) : δ 3.66 (s, 6 H); 6.5-6.83 (d, 4 H); 7.16-7.5 (d, 4 H).

Reaction of p-Bromobenzenesulfonyl chloride 1d with 6



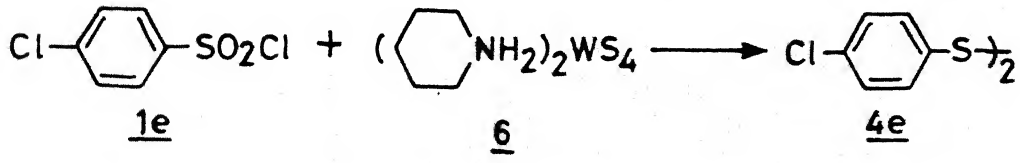
1d 6 4d

To a stirred solution of piperidinium tetrathiotungstate 6 (1.936 g, 4 mmol) in dimethyl formamide (10 ml) was added dropwise p-bromobenzenesulfonyl chloride 1d (1.02 g, 4 mmol) in dimethyl formamide (4 ml) at room temperature. The reaction took 2 h to go to completion. It was worked up the same way as described earlier. Chromatographic purification using 5% dichloromethane-petroleum ether (60-80 °C) as eluent gave bis-(p-bromophenyl)disulfide 4d (0.396 g, 53%), m.p. 91-92 °C (lit.[29] m.p. 93 °C).

IR (KBr) : 3010~3030, 1570 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 7.28-7.53 (m, 8 H).

Reaction of p-Chlorobenzenesulfonyl chloride 1e with 6



1e 6 4e

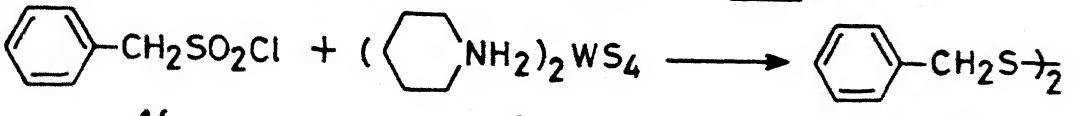
To a stirred solution of piperidinium tetrathiotungstate 6 (1.936 g, 4 mmol) in dimethyl formamide (10 ml) was added dropwise p-chlorobenzenesulfonyl chloride 1e (0.844 g, 4 mmol)

in dimethyl formamide (4 ml). The reaction was worked up as described earlier after 2 h. Chromatographic purification using 5% dichloromethane-petroleum ether (60-80 °C) as eluent gave bis(p-chlorobenzene)disulfide **4e** (0.325 g, 57%) m.p. 67-70 °C (lit.[29] m.p. 71.5 °C).

IR (KBr) : 3020, 1570, 810, 740 cm^{-1}.

^1H NMR (CCl_4) : δ 7.1-7.46 (m, 8 H).

Reaction of α-Toluenesulfonyl chloride **1f** with **6**



1f **6** **4f**

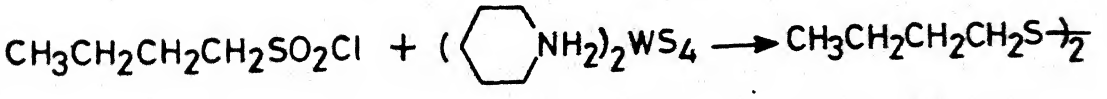
To a stirred solution of piperidinium tetrathiotungstate **6** (1.936 g, 4 mmol) in dimethyl formamide (10 ml) was added dropwise α-toluene sulfonyl chloride **1f** (0.764 g, 4 mmol) in dimethyl formamide (4 ml) at room temperature. The reaction took 4 h to go to completion. It was worked up as in the earlier case. Chromatographic purification using petroleum ether(60-80 °C) as eluent gave benzyldisulfide (0.292 g, 59%), m.p. 68-70 °C (lit.[30] m.p. 71 °C).

IR (KBr) : 3085-3030, 2930, 2000-1667, 1600, 1495, 1455, 650 cm^{-1}.

^1H NMR (CCl_4) : δ 3.5 (s, 4 H); 7.2 (s, 10 H).

MS (m/e) : 246 (M^+), 214, 182, 121, 91.

Reaction of Butanesulfonyl chloride **1g** with **6**



1g **6** **4g**

To a stirred solution of piperidinium tetrathiotungstate **6** (1.936 g, 4 mmol) in dimethyl formamide (10 ml) was added dropwise butanesulfonyl chloride **1g** (0.626 g, 4 mmol) in dimethyl formamide (4 ml) at room temperature. The reaction took 3 h to go to completion. It was worked up as described previously. Chromatographic purification using 10% ether-petroleum ether (60-80 ^{o}C) as eluent gave butyldisulfide **4g** (0.147 g, 41%), b.p. 96-99 ^{o}C/6 mm (lit.[31] b.p. 226 ^{o}C).

IR (thin film) : 2960-2860, 1465, 1450, 1375, 760 cm^{-1}.

^{1}H NMR ($CDCl_3$) : δ 0.88 (s, 6 H); 1.28-1.68 (m, 8 H), 2.70-2.96 (t, 4 H).

MS (m/e) : 178 (M^{+}), 146, 89.

Reaction of Methanesulfonyl chloride **1h** with **6**

1h **6** **4h**

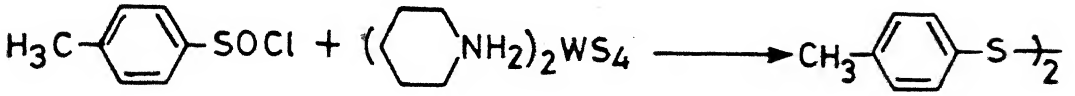
To a stirred solution of piperidinium tetrathiotungstate **6** (1.936 g, 4 mmol) in dimethyl formamide (10 ml) was added dropwise methanesulfonyl chloride **1h** (0.458 g, 4 mmol) in dimethyl formamide (2 ml) at room temperature. Reaction was complete in 3 h. Methyldisulfide **4h** was distilled out directly from the reaction mixture under vacuum. Attempts to purify dimethyldisulfide **4h** proved to be futile as dimethyl formamide contamination was there. However, G.C. analysis showed 100% conversion and dimethyldisulfide **4h** as the only product; b.p.

108-109 °C (lit.[32] b.p. 40 °C/12 mm).

IR (thin film) : 2960, 2856, 1375 cm^{-1}.

^1H NMR (CCl_4) : δ 2.43 (S, 6 H).

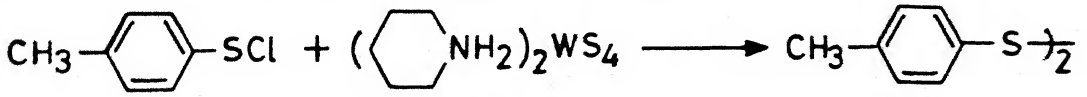
Reaction of p-Toluenesulfinyl chloride 2 with 6



2 6 4b

To a stirred solution of piperidinium tetrathiotungstate 6 (1.936 g, 4 mmol) in dimethyl formamide (10 ml) was added dropwise a solution of p-toluenesulfinyl chloride 2[33] (0.698 g, 4 mmol) in dimethyl formamide (4 ml) at room temperature. The reaction was complete in 0.5 h. The reaction was worked up in the same way as described earlier. Chromatographic purification using petroleum ether (60-80 °C) as eluent gave p-tolyldisulfide 4b (0.473 g, 96%), m.p. 44 °C (lit.[29] m.p. 46 °C).

Reaction of p-Toluenesulfenyl chloride 3 with 6

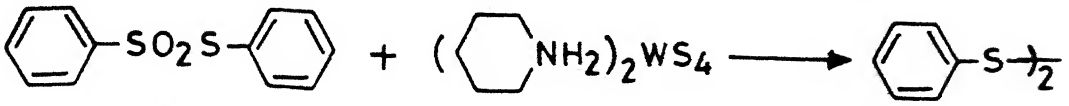


3 6 4b

To a stirred solution of piperidinium tetrathiotungstate 6 (0.968 g, 2 mmol) was added dropwise a solution of freshly prepared p-toluenesulfenyl chloride[34] 3 (0.317 g, 2 mmol) in dimethylformamide (4 ml) at room temperature. The reaction was

complete in 0.5 h and was worked up as described previously. Chromatographic purification using petroleum ether (60-80 °C) as eluent gave p-tolyldisulfide (0.215 g, 88%), m.p. 43-44 °C (lit.[29] m.p. 46 °C).

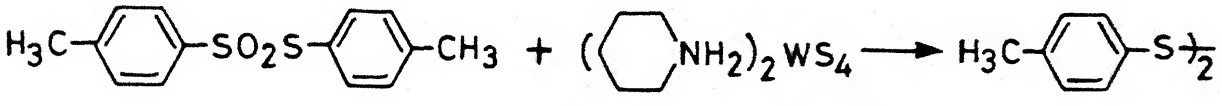
Reaction of Phenylbenzenethiolsulfonate **5a** with **6**



5a **6** **4a**

To a stirred solution of piperidinium tetrathiotungstate (1.936 g, 4 mmol) in dimethyl formamide (10 ml) was added dropwise a solution of phenylbenzenethiolsulfonate **5a** (1.0 g, 4 mmol). The reaction was allowed to go for 0.5 h. It was worked up the same way as described earlier. Chromatographic purification using 4:1 hexane-benzene as eluent gave phenyldisulfide **4a** (0.583 g, 67%), m.p. 58-59 °C (lit.[29] m.p. 60 °C).

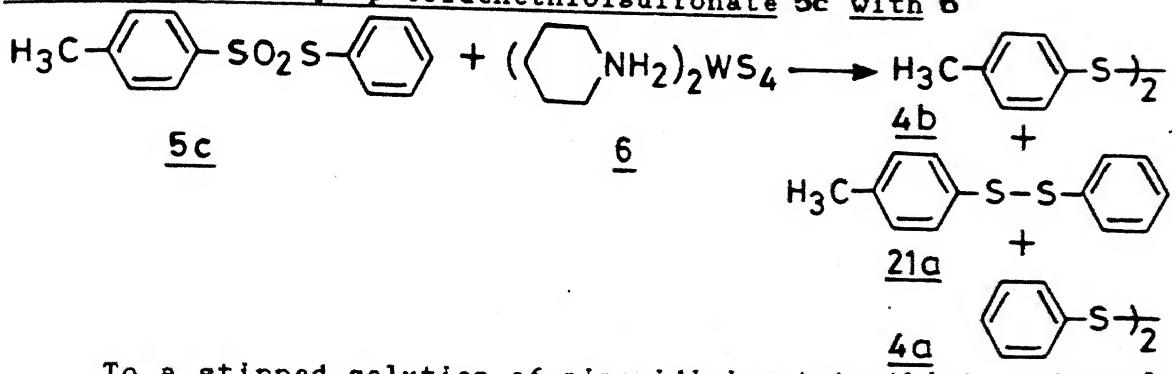
Reaction of p-Tolyl-p-toluenethiolsulfonate **5b** with **6**



5b **6** **4b**

To a stirred solution of piperidinium tetrathiotungstate **6** (1.936 g, 4 mmol) in dimethyl formamide (10 ml) was added dropwise a solution of p-tolylthiolsulfonate **5b** (1.112 g, 4 mmol) in dimethyl formamide (4 ml). After 0.5 h the reaction mixture was worked up as described earlier. Chromatographic purification using petroleum ether (60-80 °C) as eluent gave p-tolyldisulfide **4b** (0.900 g, 92%), m.p. 44 °C.

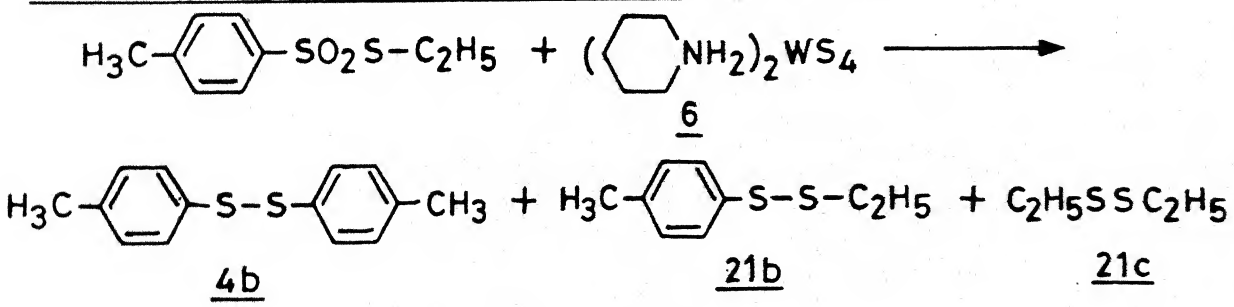
Reaction of Phenyl p-toluenethiolsulfonate **5c** with **6**



5c **6** **4b** **21a** **4a**

To a stirred solution of piperidinium tetrathiotungstate **6** (1.936 g, 4 mmol) in dimethyl formamide (10 ml) was added dropwise a solution of phenyl p-toluenethiolsulfonate **5c** (1.056 g, 4 mmol). The reaction took 0.5 h to go to completion to give a mixture of the three disulfides; p-tolylphenyl disulfide **21a**, phenyl disulfide **4a** and tolyl disulfide **4b** in a ratio of 2:1:1 (as determined by gas chromatography) in an overall yield of 84%. Gas chromatography: column OV 17, N_2 and H_2 50 mL/min. column temp. 200 °C, injection temp. 280 °C, **4b** (t_R: 1.138); **4a** (t_R: 1.767), **21a** (t_R: 7.023).

Reaction of p-Tolylethanethiolsulfonate **5d** with **6**

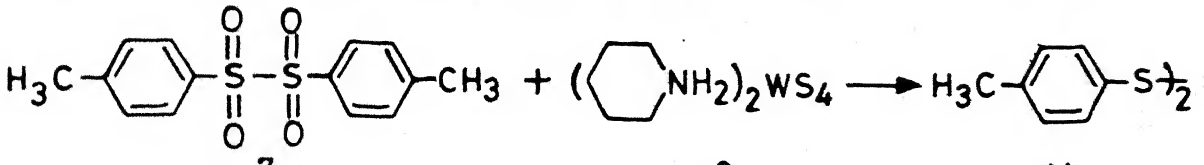


6 **4b** **21b** **21c**

To a stirred solution of piperidinium tetrathiotungstate

(1.936 g, 4 mmol) in dimethyl formamide (10 ml) was added dropwise a solution of p-tolylethanethiolsulfonate **5d** (0.864, 4 mmol). The reaction took 1 h to go to completion. It was worked up as described earlier. It gave a mixture of three disulfides, p-tolyl disulfide **4b**, p-tolylethyl disulfide **21b** and diethyl disulfide **21c** in a 1:2:1 ratio in an overall yield of 58%. The disulfides were compared with authentic samples of the same.

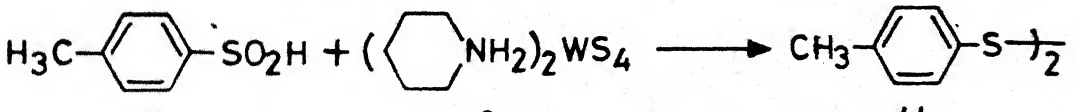
Reaction of p-Tolyldisulfone **7** with **6**



7 **6** **4b**

To a stirred solution of piperidinium tetrathiotungstate **6** (1.936 g, 4 mmol) in dimethyl formamide (10 ml) was added dropwise a solution of p-tolyldisulfone **7** (1.240 g, 4 mmol) in dimethyl formamide (4 ml) at room temperature. The reaction took 12 h to go to completion. It was worked up as described earlier. Chromatographic purification using petroleum ether (60-80 °C) as eluent gave p-tolyldisulfide **4b** (0.863 g, 88%), m.p. 44 °C (lit.[29] m.p. 46 °C).

Reaction of Toluenesulfinic acid **16** with **6**



16 **6** **4b**

To a stirred solution of piperidinium tetrathiotungstate **6**

(1.936 g, 4 mmol) in dimethyl formamide (10 ml) was added dropwise with constant stirring p-toluenesulfinic acid 16 (0.624 g, 4 mmol) in dimethyl formamide (4 ml) at room temperature. The reaction took 0.5 h to go to completion. It was worked up as described earlier. Chromatographic purification using petroleum ether (60-80 ^{o}C) as eluent gave p-tolyldisulfide (0.483 g, 98%), m.p. 44 ^{o}C (lit.[29] m.p. 46 ^{o}C).

3.4 REFERENCES

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CHAPTER IV

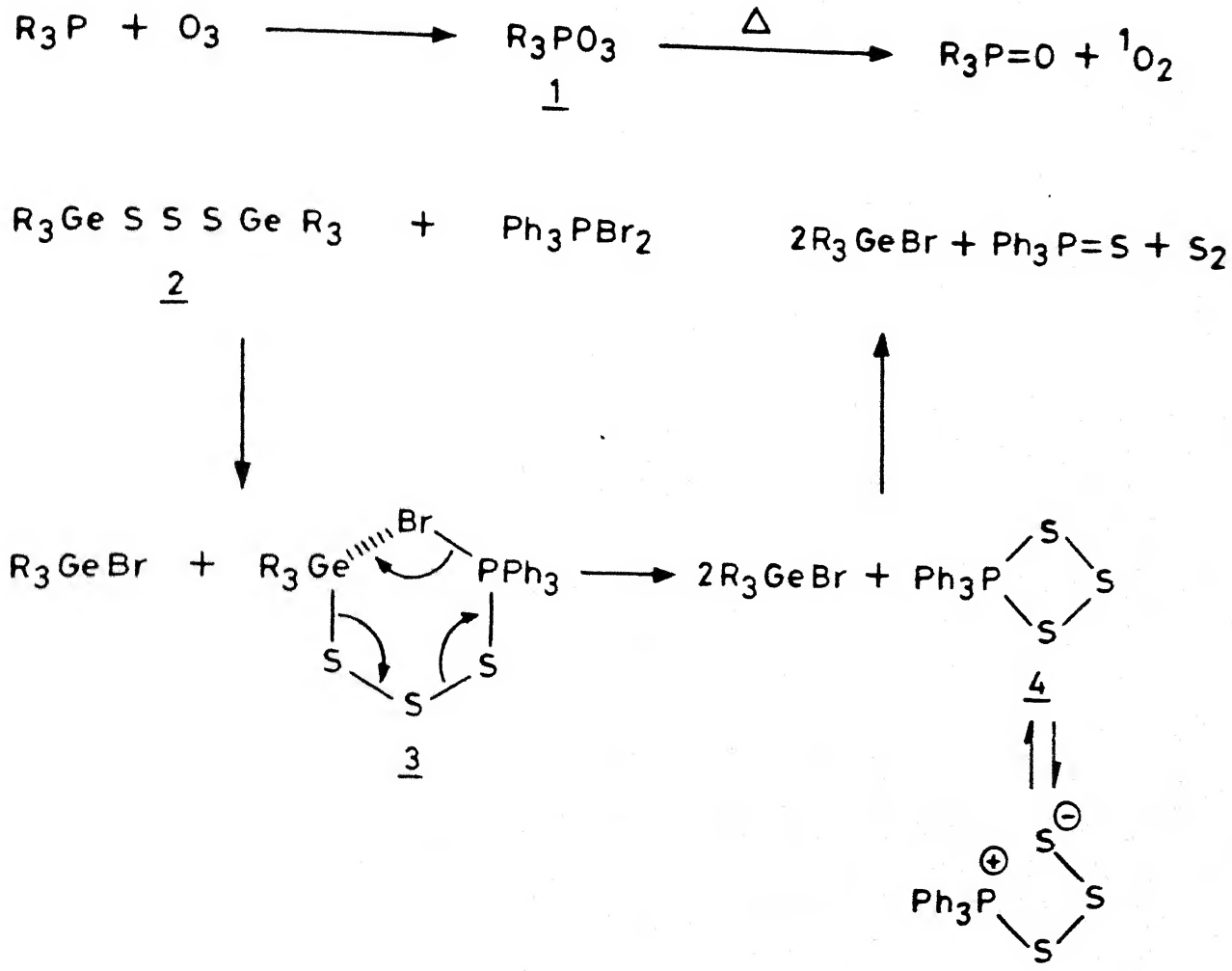
CHEMISTRY OF SINGLET-SULFUR

4.1 INTRODUCTION

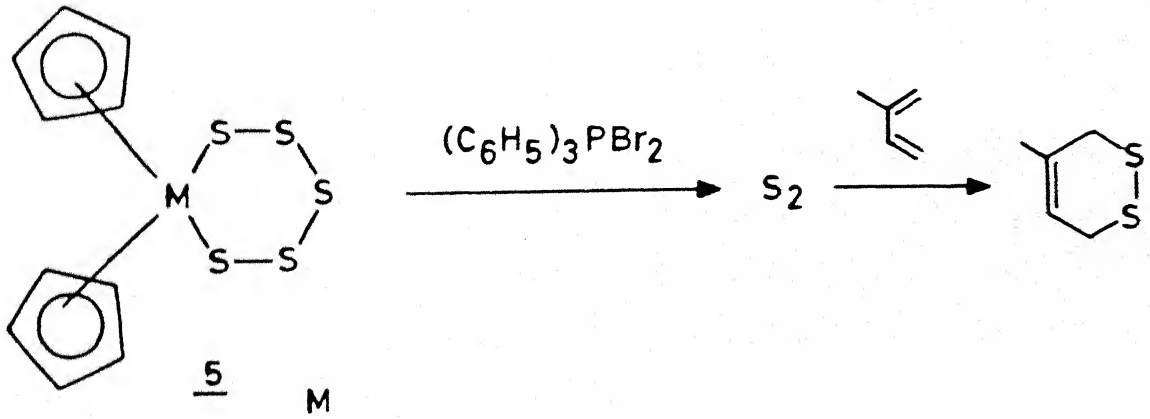
Although reference to singlet oxygen ($^1O_2$) first appeared in the literature in 1924, it is primarily during the past two decades most of its chemistry has been delineated.[1] For several years now, in anticipation that singlet sulfur ($^1S_2$) might emulate singlet oxygen chemistry, a number of workers have been actively pursuing possible synthetic avenues for its preparation. Among the many procedures available for the generation of singlet oxygen ($^1O_2$),[1,2] one of the most attractive is by means of the controlled, thermally induced decomposition of a phosphine or phosphite/ozone adduct (**Scheme 4.1**). The first chemical generation of diatomic sulfur ($^1S_2$) was achieved only in 1984 by Steliou,[3] by the decomposition of a germanium trisulfide species **2** with triphenylphosphine dibromide. Evidence for the existance of singlet diatomic sulfur was accomplished by Diels-Alder trapping with various dienes to afford cyclic disulfides in isolated yields ranging from 20% to 50% (**Scheme 4.1**).

In an analogous reaction, Harpp and MacDonald[4] discovered that a series of metal-pentasulfides **5**, on treatment with triphenylphosphine dibromide, afford a S_2 (likely $^1S_2$). The

Scheme-4.1



Scheme-4.2



5

M

a, Ti

b, Zr

yield of cyclic disulfides obtained by trapping singlet sulfur in this reaction with 1,3-dienes is less than that obtained from the decomposition of germanium trisulfide **2**. The reaction with **5c**, however, did not give any disulfide (**Scheme 4.2**).

In 1987, Steliou and coworkers reported an improved method for the production of singlet diatomic sulfur using a biphenyl precursor.[5] In the presence of B_2S_3, generated *in situ*, 2,2-dibenzoylbiphenyl **7** with *bis*(trimethylsilyl)sulfide and boron trichloride affords 2,2'-*bis*(thiobenzoyl)biphenyl **9**, which spontaneously ejects S_2 with C-C coupling and formation of 9,10-diphenylphenanthrene **11** (**Scheme 4.3**).

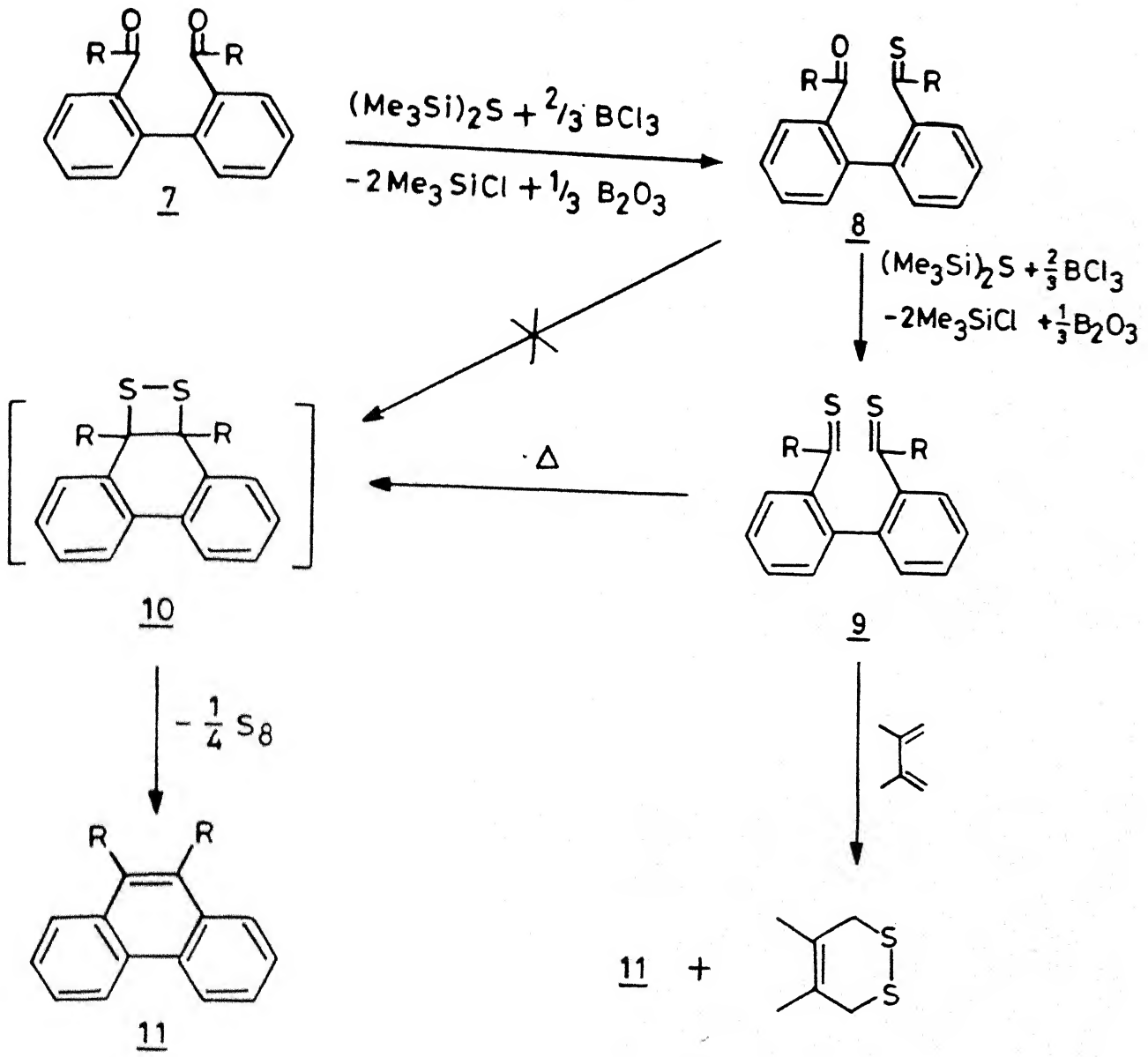
These efforts have stimulated considerable interest in this area, and during the past year or so variety of groups have investigated some aspects of the chemistry of diatomic sulfur that began nearly 25 years ago.[1]

Recently, Schmidt found that cyclic 5,5-dimethyl-1,2-dithia-3,7-diselenacycloheptane **12** undergoes thermal decomposition with ring contraction and formation of 4,4-dimethyl-1,2-di-selenacyclopentane **13** and S_2. This was trapped to give modest yields of cyclic disulfides[6] (**Scheme 4.4**).

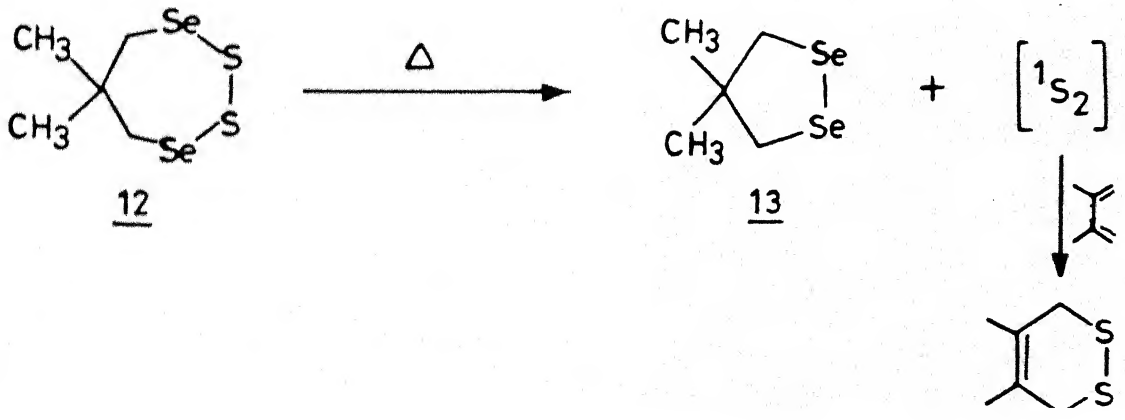
Ando has implicated the formation of singlet diatomic sulfur in the decomposition of 9,10-epidithio-9,10-dihydroanthracene (anthracene endodisulfide). His strategy to prepare this disulfide **18** is rather circuitous[7] (**Scheme 4.5**).

In the course of some preliminary investigations on the

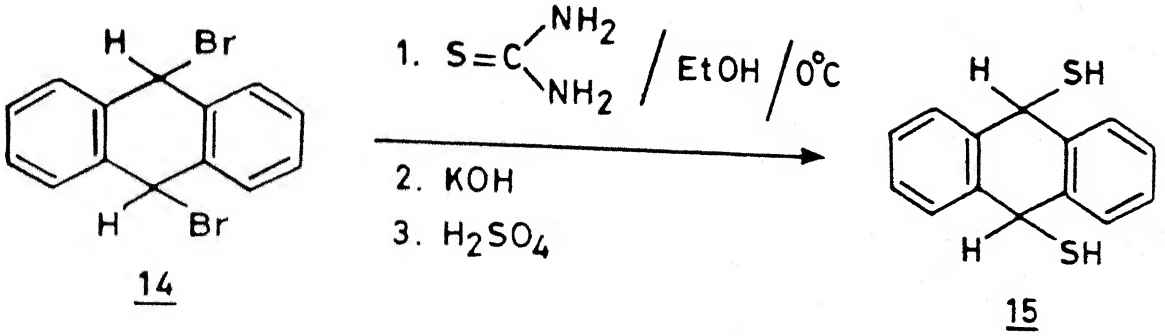
Scheme - 4.3



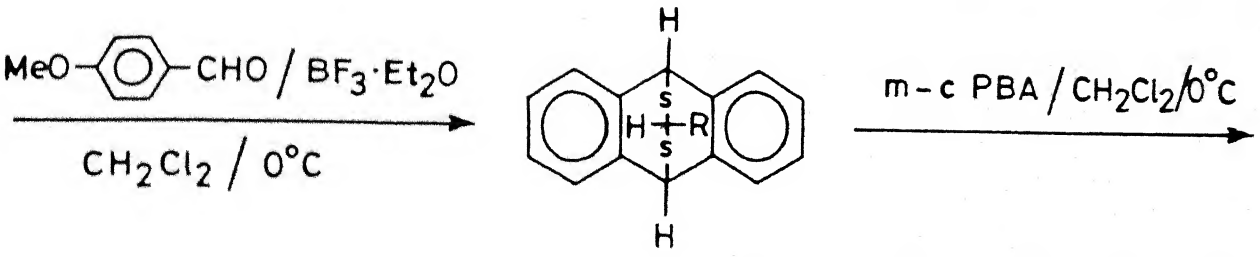
Scheme - 4.4



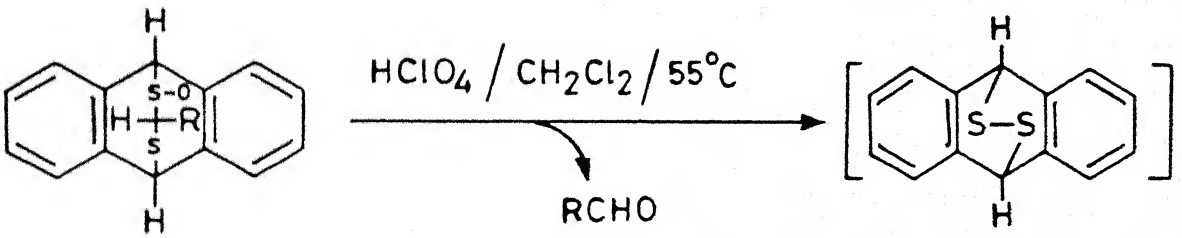
Scheme-4.5



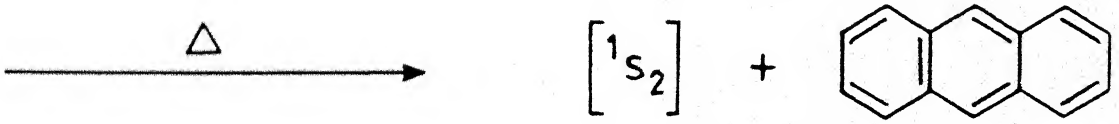
14 15



16



17 18



19

chemistry of tetrathiomolybdates and tetrathiotungstates, we isolated elemental sulfur in some reactions. It is believed that the formation of elemental sulfur from these polysulfide complexes would go *via* the intermediacy of reactive singlet sulfur. If it is so, then reaction in the presence of conjugated dienes should suppress the formation of elemental sulfur with concomitant formation of the corresponding Diels-Alder adducts from the addition of S_2 unit to the diene. The reaction of tetrathiomolybdates and tungstates was explored for this purpose. It appeared reasonable that we would be able to develop a shorter route to Ando's key *endo* disulfide intermediate **18** *via* the novel alkylation of tetrathiometallates **6** with alkyl halide reported earlier (**Chapters 1 and 2**).

4.2 RESULTS AND DISCUSSION

Generation of Singlet Sulfur ($^1S_2$) Using Tetrathiotungstates, and its Reactions

Although singlet diatomic sulfur has been known to exist in molten sulfur and vaporised sulfur,[8] relatively few studies on its chemistry have been reported because of no convenient method of generation under mild conditions in liquid phase.[3,5] Very recently Andō[7] reported the generation of singlet diatomic sulfur from 9,10-epidithio-9,10-dihydroanthracene **18**. Compound **18** itself was prepared *in situ* by a rather circuitous route starting from 9,10-dibromo-9,10-dihydroanthracene **14** (**Scheme 4.5**). Since there was no efficient, direct method for

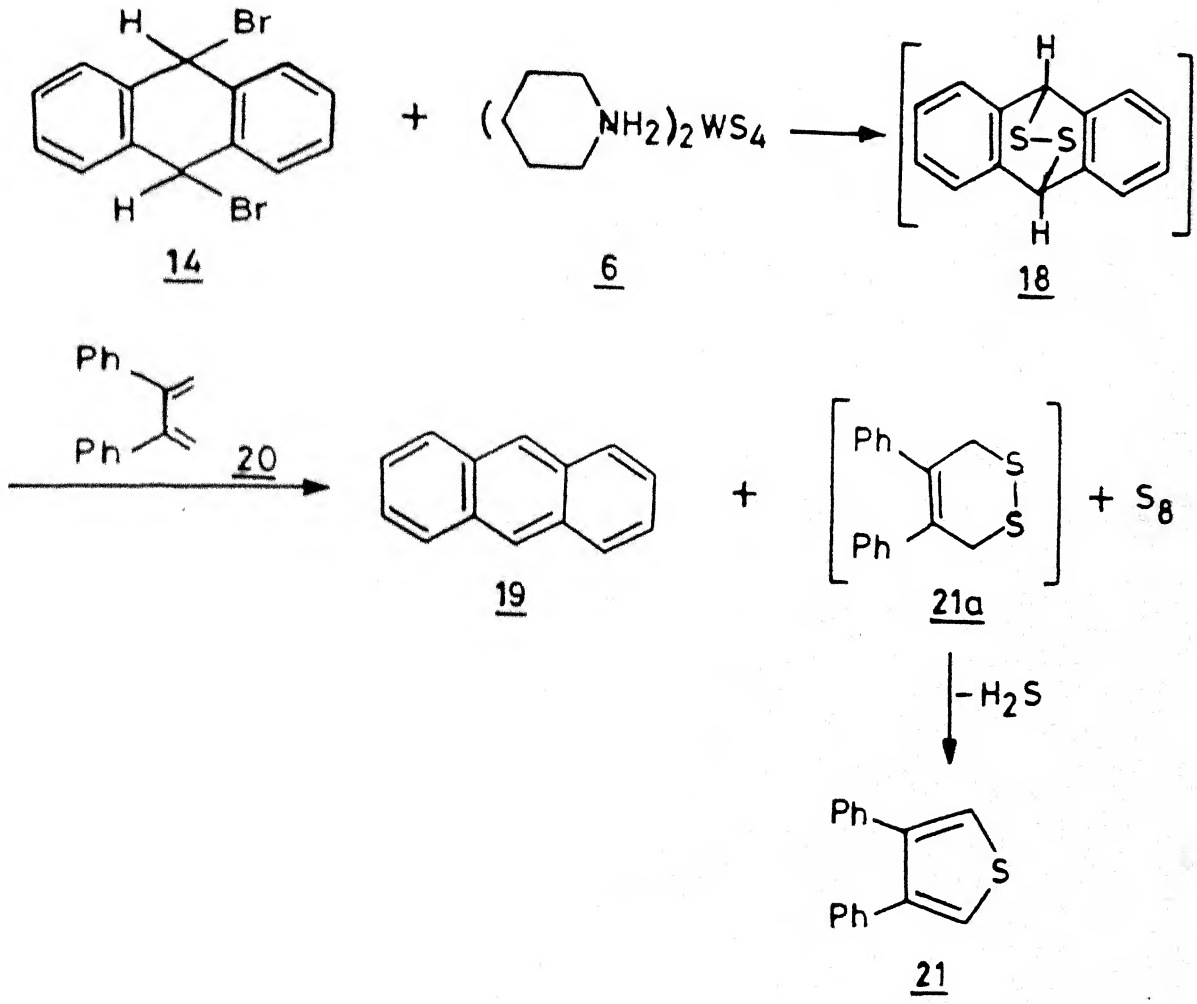
the conversion of either the dibromide **14** or the dithiol **15** to the endo-disulfide **18**, Ando had to resort to a long synthetic sequence.

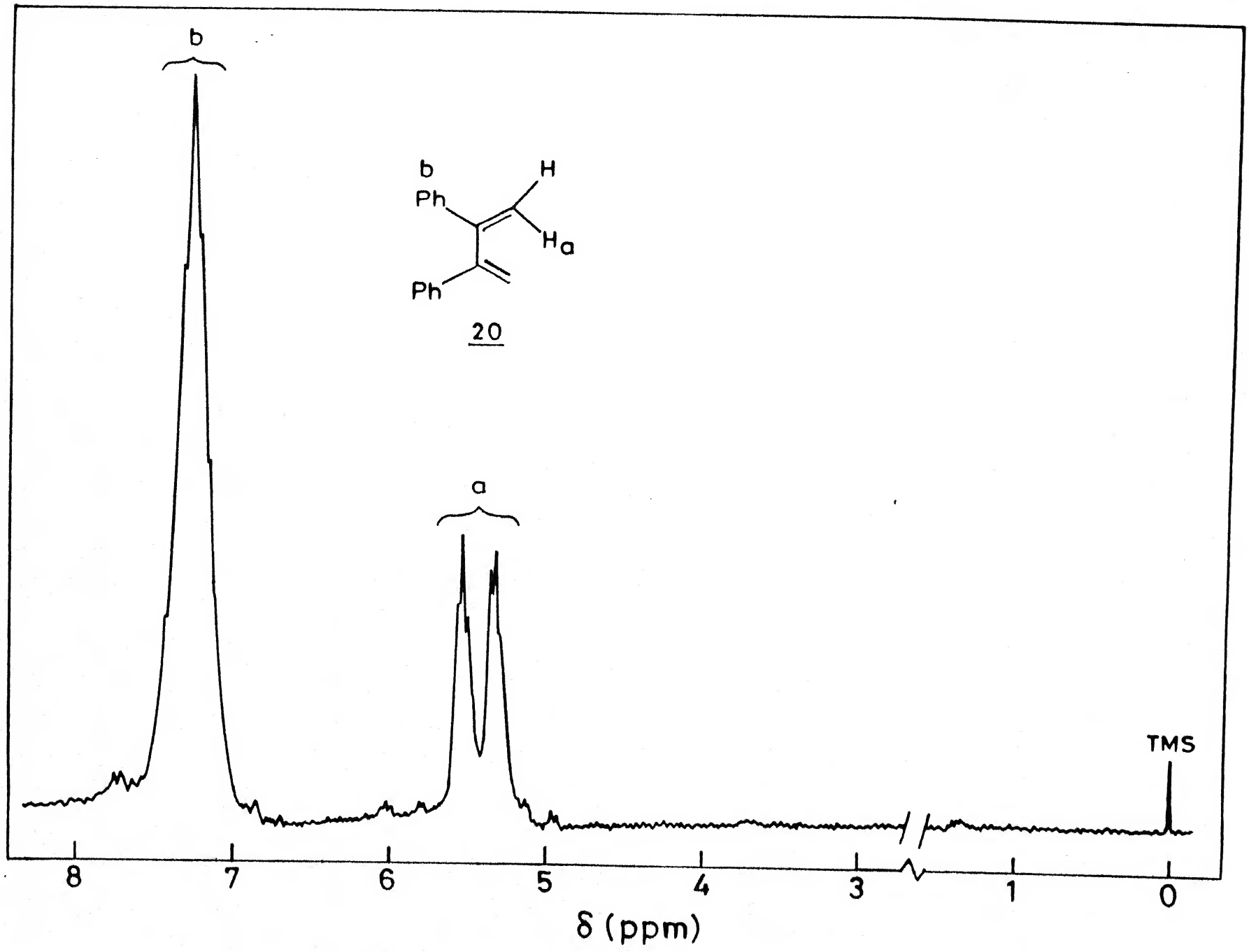
Since we have shown earlier (**Chapters 1 and 2**) that piperidinium tetrathiotungstate **6** is a convenient reagent for the synthesis of acylic and cyclic disulfides under very mild reaction conditions, it appeared reasonable that we would be able to develop a shorter route to Ando's key endo-disulfide intermediate **18**.

Accordingly, a reaction was performed initially where dibromo-compound[9] **14** was treated with tetrathiotungstate **6** (DMF 28 ^{o}C, 4 h). The endo-sulfide **18** could not be isolated, but we obtained anthracene **19** and elemental sulfur (S_8). Obviously the endo-disulfide **18** formed in the reaction decomposed to give anthracene and singlet diatomic sulfur which in the absence of any trapping agent got converted to sulfur.

Singlet diatomic sulfur produced in a reaction has been trapped with conjugated dienes by Ando[7] and others.[3-6] In order to show that an active singlet diatomic sulfur ($^1S_2$) is produced in our reaction with tetrathiotungstate **6**, the dibromo compound **14** was treated with **6** in the presence of 2,3-diphenyl-1,3-butadiene **20** (DMF, 80 ^{o}C, 4 h). The products isolated from this reaction are anthracene (90%), elemental sulfur and 3,4-diphenylthiophene **21** (11%) (**Scheme 4.6**). It is not surprising that we could not isolate the 1,2-dithiin **21a**, since **21a** is known to be unstable and it decomposes to **21** by

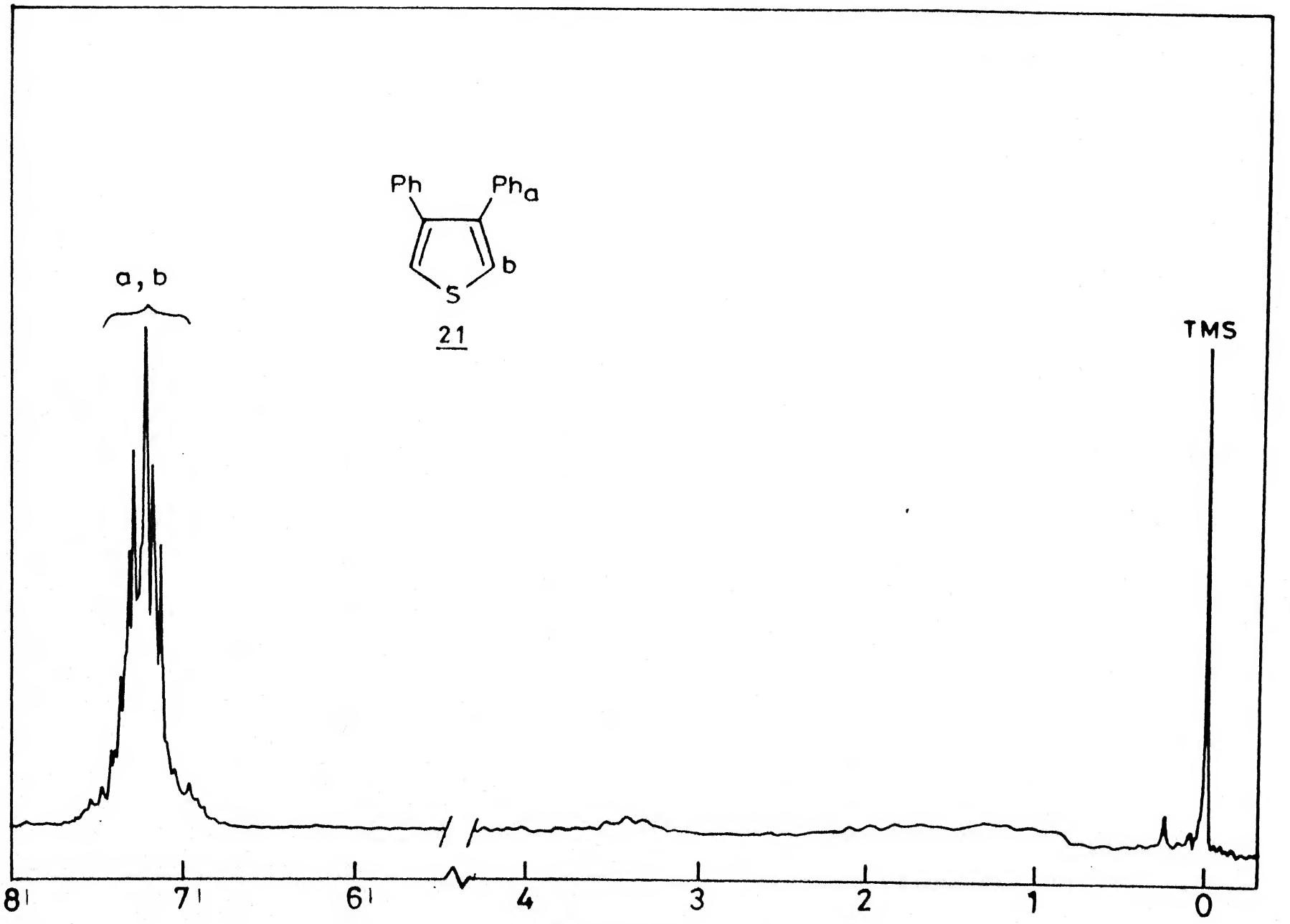
Scheme - 4.6


H
Br
H
Br
14
+
(NH2)2WS4
6
H
S–S
H
18
Ph
Ph
20
19
+
Ph
S
S
Ph
21a
+ S8
-H2S
Ph
S
Ph
21



20

^{1}H NMR spectrum (90 MHz) of 20



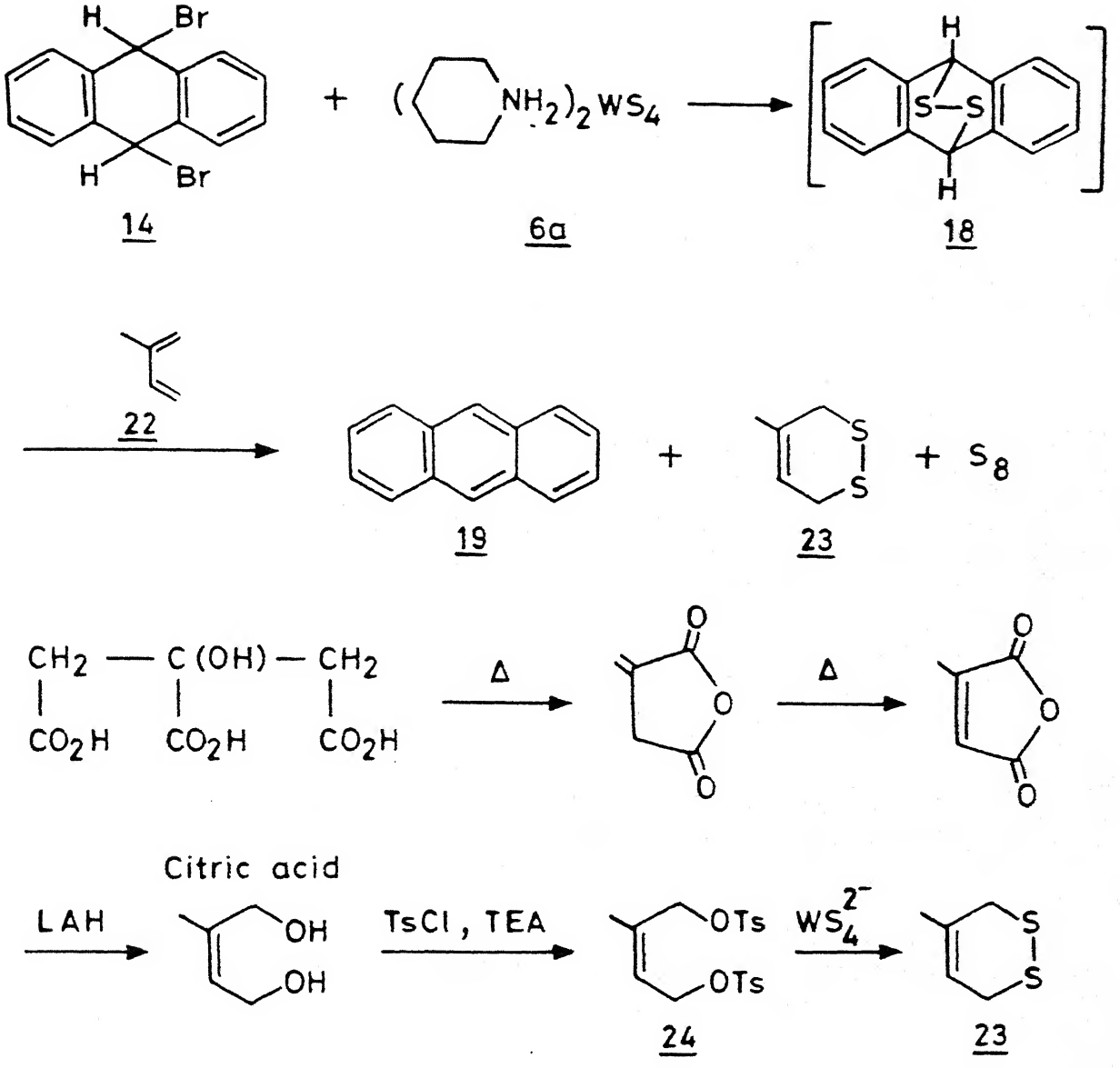
^{1}H NMR spectrum (80 MHz) of 21

elimination of hydrogen sulfide under the reaction conditions.[7]

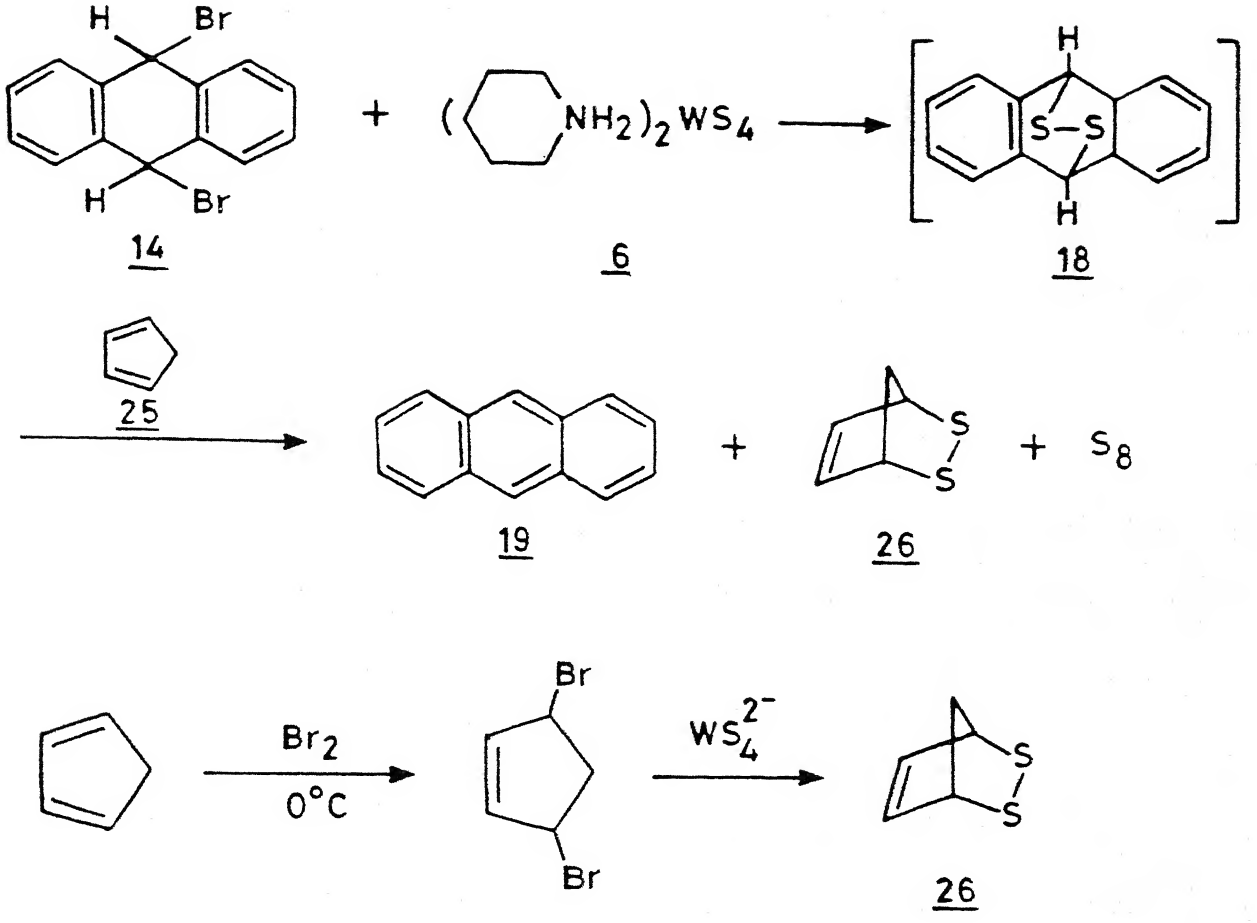
Similarly the reaction of dibromide **14** with **6** in the presence of 2-methylbutadiene **22** (DMF, 80 °C, 2 h) led to the formation of anthracene (88%), sulfur and the dithiin **23** (4%) (**Scheme 4.7**). The same dithiin **23** could also be obtained by another route involving tetrathiotungstate (**Chapter 2**),for comparison. Thus the allylic ditosylate **24** on treatment with tetrathiotungstate **6** (DMF, 28 °C, 18 h) afforded the disulfide **23** (43%).

In another reaction the singlet diatomic sulfur was trapped using cyclopentadiene (DMF, ~28 °C, 4 h). In this case also, apart from anthracene (90%) and sulfur, the disulfide **26** was obtained (7%) (**Scheme 4.8**). The same disulfide **26** was obtained by an independent route using tetrathiotungstate **6** and 3,5-dibromocyclopentene (DMF, 0 °C, 12 h) (20%) (**Chapter 2**). In our study, the yields refer to isolated products whereas previous workers have reported the yield of Diels-Alder adducts based on anthracene formed from **14**. It is obvious that the trapping efficiency of these dienes has been poor and hence the low yield of the Diels-Alder adducts. Another factor that would account for the low yield of the products in all these reactions could be the inherent instability of these cyclic, allylic disulfides which tend to polymerize. Since elemental sulfur itself does not form the Diels-Alder adducts under our reaction conditions,the intermediacy of an active singlet diatomic sulfur is proposed in our reaction with tetra-

Scheme-4.7


H
Br
H
Br
14
+
$(NH_2)_2WS_4$
6a
H
S—S
H
18
22
19
+
S
S
23
+ S_8
CH_2 — C(OH) — CH_2
CO_2H CO_2H CO_2H
Δ
O
O
O
Δ
O
O
O
Citric acid
LAH
OH
OH
TsCl, TEA
OTs
OTs
24
WS_4^{2-}
S
S
23

Scheme - 4.8



thiotungstate 6.

Further work obviously is needed to improve the efficiency of this process. In the present methodology the conditions need to be optimized and one has to also look for other substituted anthracene derivatives as possible precursors to singlet diatomic sulfur.

4.3 EXPERIMENTAL

Experimental Procedure

All the reactions were performed in oven dried apparatus. Reaction mixtures were stirred magnetically unless otherwise specified and all the reactions were carried out in the dark. Reaction product solutions were concentrated using a Perfit rotary evaporator and products were characterized by comparison with authentic samples (spectra, T.L.C., m.p.). Lassaigne's test was performed on each compound for detection of sulfur.

Materials

Commercial grade solvents were distilled prior to use. Dimethyl formamide was initially purified by azeotropic distillation with benzene. The residual solvent was shaken with calcium oxide, filtered and distilled at reduced pressure. The fraction having b.p. 76 ^{o}C/39 mm Hg was collected. The distillate was stored over type 4 Å molecular sieves.

Chromatography

Analytical thin layer chromatography was performed on Merck precoated glass backed silica gel 60F-254 0.25 mm plates. Visualization of the spots was effected by one or more of the following techniques:(a) ultraviolet illumination; (b) exposure to iodine vapour; (c) immersion of the plate in a 10% solution of phosphomolybdic acid in ethanol followed by heating to ca. 200 ^{o}C.

Column chromatography was performed using 60-120 and 100-200 mesh Acme silica gel. The flash chromatography was performed using Merck thin-layer chromatography silica gel.

Physical Data

Melting points (m.p.) were determined with a uni-melt capillary melting point apparatus and are uncorrected. Boiling points (b.p.) are uncorrected.

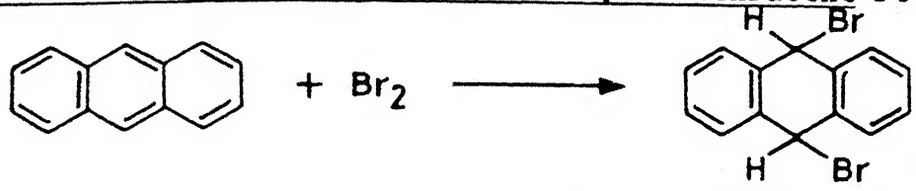
Bulb to bulb distillation was carried out on a Büchi-GKR-50 distillation unit.

Infrared (IR) spectra were recorded on Perkin-Elmer model 1320 and 580 spectrophotometers and are reported in wave numbers (cm^{-1}).

Proton magnetic resonance (PMR) spectra were recorded at 90 MHz on a Varian EM-390 instrument, at 80 MHz on Bruker WP-80 instrument and at 90 MHz on Jeol FX-90Q instrument. Chemical shifts are reported in parts per million down field from internal reference tetramethyl silane (TMS) (δ). Multiplicity

is indicated using the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad); etc. Mass spectra (MS) were recorded on a Jeol JMS D-300 mass spectrometer. Principal molecular fragments are reported.

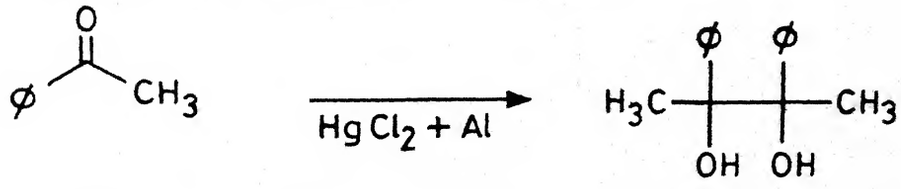
Preparation of 9,10-Dibromo-9,10-dihydroanthracene 14



14

A solution of Br_2 (0.5 ml) in CS_2 (10 ml) was slowly added to finely powdered anthracene (1.78 g, 10 mmol) suspended in CS_2 (20 ml) and the reaction mixture was cooled in a freezing mixture. After 0.5 h the solid that separated was collected and washed with cold CS_2 and with cold ether; yield (3.2 g, 94%), m.p. 168-170 °C (lit.[9] m.p. 179 °C).

Preparation of 2,3-Diphenyl-2,3-butanediol



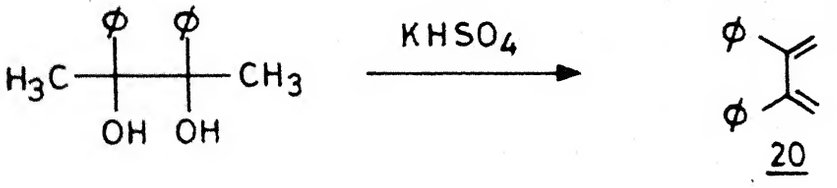
Pinacolic reduction of acetophenone (9.55 g, 0.0795 mol) in absolute ethanol (39 ml) - benzene (39 ml) solution with aluminium foil (2.4 g, 0.0890 g-atom) in the presence of small amount of mercuric chloride (0.150 g, 0.55 mmol) according to the procedure of Newman[10] gave a thick oil. This was triturated with petroleum ether (40-60 °C) (10 ml). The resulting white solid was collected on a Buchner funnel and was

washed with petroleum ether (40-60 °C) (3 ml) giving 2,3-diphenyl-2,3-butanediol as white solid; m.p. 74-85 °C (lit.[11] m.p. 74-85 °C).

IR (KBr) : 3375, 3080, 2970, 1600 cm^{-1}.

^1H NMR (CCl_4) : δ 1.37, 1.42 (2s, 6 H), 2.37, 2.85 (2br,s, 2 H), 7.10- 7.15 (br,s, 10 H).

Preparation of 2,3-Diphenyl-1,3-butadiene **20**



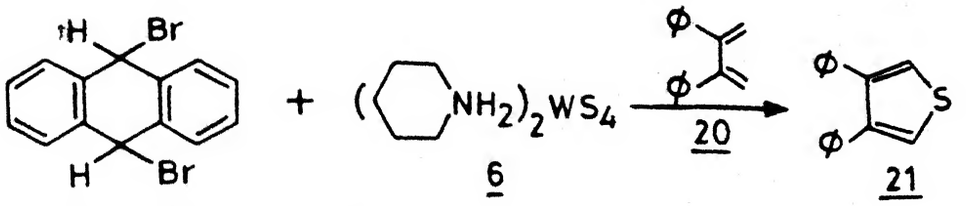
20

2,3-Diphenyl-2,3-butanediol (5.0 g, 0.2 mol) was mixed with powdered and freshly fused potassium bisulfate (0.125 g, 0.92 mmol). The mixture was distilled at 13 mm by gradual heating with an oil-bath to a final bath temperature of 210 °C. Heating had to be controlled very carefully between 160-180 °C. The product distilled between 145 and 170 °C (13 mm) and had a tendency to solidify in the condenser. The distillation took 2.5 h. The distillate was cooled in a freezer (-15 °C). It was then slowly warmed to room temperature and filtered giving 2,3-diphenylbutadiene **20** as a white crystalline solid (1.04 g, 75%); m.p. 41-46 °C (lit.[11] m.p. 46 °C).

IR ($CHCl_3$) : 3010, 1650 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 5.25, 5.47 (d, 4 H); 7.03-7.47 (br,s 10 H).

Reaction of compound **20** with **6**



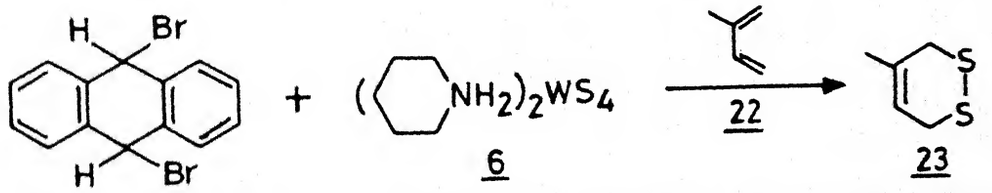
To a stirred solution of piperidinium tetrathiotungstate **6** (1.936 g, 4 mmol) in dimethyl formamide (12 ml) was added **20** (0.392 g, 4 mmol) at room temperature. To the resulting solution was added dropwise 9,10-dibromo-9,10-dihydroanthracene (1.352 g, 4 mmol) in dimethyl formamide (15 ml). After the addition was complete, the reaction mixture was heated at 80 °C for 4 h. It was worked up by diluting the reaction mixture by water (150 ml) and extracting it with petroleum ether (40-60 °C) (5x25 ml). The solvent was removed under reduced pressure. Column chromatography using petroleum ether (60-80 °C) as eluent yielded **21** (0.106 g, 11%), m.p. 110-112°C (lit.[12] m.p. 114 °C). .

IR (KBr) : 1460, 850, 795, 770, 750, 730, 720, 687 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 7.15-7.25 (m, 12 H)

MS (m/e) : 236 (M^+).

Reaction of 2-Methylbutadiene **22** with **6**



To a stirred solution of piperidinium tetrathiotungstate **6** (1.936 g, 4 mmol) in dimethyl formamide (12 ml) was added 2-methylbutadiene **22** (0.272 g, 4 mmol) at room temperature. To the resulting solution was added dropwise 9,10-dibromo-9,10-dihydroanthracene (1.352 g, 4 mmol) in dimethyl formamide (15

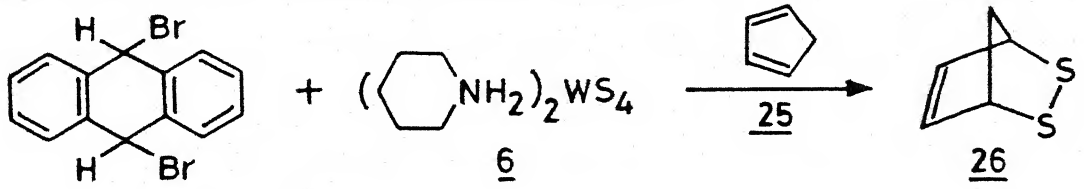
ml). After the addition was complete, the reaction was allowed to stir for 2 h at 80 °C. It was worked up the same way as described earlier. Column chromatography using petroleum ether (40-60 °C) as eluent gave compound **23** (0.021 g, 4%). This compound was found to be identical to that obtained by treating ditosylate **24** with piperidinium tetrathiotungstate.

IR ($CHCl_3$) : 3010, 2970, 1600 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.72 (s, 3 H); 3.10-3.14 (m, 4 H); 5.06 (t, 1 H).

MS (m/e) : 132 (M^+).

Reaction of Cyclopentadiene **25** with **6**



To a stirred solution of piperidinium tetrathiotungstate **6** (1.936 g, 4 mmol) in dimethyl formamide (12 ml) was added cyclopentadiene **25** (0.264 g, 4 mmol) at room temperature. To the resulting solution was added dropwise 9,10-dibromo-9,10-dihydroanthracene (1.352 g, 4 mmol) in dimethyl formamide (15 ml). After the addition was complete, the reaction was allowed to stir at room temperature for 4 h. It was worked up the same way as described earlier. Column chromatography using pentane as eluent afforded the bicyclic disulfide **26** (0.036 g, 7%) as a waxy solid which was found to be identical to that obtained by treating 3,5-dibromocyclopentene with piperidinium tetrathiotungstate.

IR ($CHCl_3$) : 3010, 1600 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 2.47 (s, 1 H); 2.81 (s, 1 H); 4.17-4.3 (br,s, 2 H); 5.68 (br, 2 H).

MS (m/e) : 130 (M^+).

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